Is it cerebral or renal salt wasting?

John K. Maesaka[1,2], Louis J. Imbriano[1,2], Nicole M. Ali[1,2] and Ekambaram Ilamathi[1,2]

[1]*Division of Nephrology and Hypertension, Department of Medicine, Winthrop-University Hospital, Mineola, New York, USA and* [2]*SUNY Medical School at Stony Brook, Stony Brook, New York, USA*

Cerebral salt-wasting (CSW), or renal salt-wasting (RSW), has evolved from a misrepresentation of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) to acceptance as a distinct entity. Challenges still confront us as we attempt to differentiate RSW from SIADH, ascertain the prevalence of RSW, and address reports of RSW occurring without cerebral disease. RSW is redefined as 'extracellular volume depletion due to a renal sodium transport abnormality with or without high urinary sodium concentration, presence of hyponatremia or cerebral disease with normal adrenal and thyroid function.' Our inability to differentiate RSW from SIADH lies in the clinical and laboratory similarities between the two syndromes and the difficulty of accurate assessment of extracellular volume. Radioisotopic determinations of extracellular volume in neurosurgical patients reveal renal that RSW is more common than SIADH. We review the persistence of hypouricemia and increased fractional excretion of urate in RSW as compared to correction of both in SIADH, the appropriateness of ADH secretion in RSW, and the importance of differentiating renal RSW from SIADH because of disparate treatment goals: fluid repletion in RSW and fluid restriction in SIADH. Patients with RSW are being incorrectly treated by fluid restriction, with clinical consequences. We conclude that RSW is common and occurs without cerebral disease, and propose changing CSW to RSW.

Kidney International (2009) **76,** 934–938; doi:10.1038/ki.2009.263; published online 29 July 2009

KEYWORDS: cerebral/renal salt wasting; fractional phosphate excretion; fractional urate excretion; hyponatremia; SIADH

Correspondence: *John K. Maesaka, Division of Nephrology and Hypertension, Department of Medicine, Winthrop-University Hospital, 200 Old Country Road, Suite 135, Mineola, New York 11501, USA.*
E-mail: jmaesaka@winthrop.org

Received 16 March 2009; revised 12 May 2009; accepted 16 June 2009; published online 29 July 2009

OBJECTIVES

Cerebral salt wasting (CSW) or, more appropriately, renal salt wasting (RSW), is a syndrome with a controversial history that evolved from a misrepresentation of inappropriate secretion of antidiuretic hormone (SIADH) to acceptance as a distinct entity. Challenges confront us as we attempt to find clues to differentiate RSW from SIADH, ascertain the prevalence of RSW, and address reports of RSW occurring without cerebral disease.[1,2] The objectives of this mini review are to redefine RSW, explain how this controversy evolved, emphasize the appropriateness of antidiuretic hormone (ADH) secretion in RSW, differentiate RSW from SIADH by the persistence of hypouricemia and increased fractional excretion (FE) of the urate after correction of hyponatremia in RSW, stress the clinical importance of differentiating RSW from SIADH because of divergent therapeutic goals of fluid repletion in RSW or fluid restriction in SIADH, and advocate changing CSW to RSW.

DEFINITION OF RSW: EVOLUTION OF CONTROVERSY

RSW is defined as, 'extracellular volume (ECV) depletion due to a renal sodium transport abnormality with or without high urinary sodium concentration (UNa), presence of hyponatremia, or cerebral disease with normal adrenal and thyroid function'. Although this definition delineates the salient features of RSW, its existence has been an enduring controversy since the seminal description of SIADH.[3] The previous report of CSW was based on an inappropriately high urine chloride of 61.6 mmol/l in a clinically 'dehydrated' patient with cerebral disease.[4] As volume-depleted patients with normal kidneys avidly conserve salt, the urine chloride of 61.6 mmol/l was best explained by RSW.[5] When Schwartz *et al.*[3] encountered patients who mimicked normal individuals receiving exogenous ADH, it became apparent that an euvolemic hyponatremic patient can present with high UNa without implicating RSW. As the diagnosis of 'dehydration' was made by inaccurate clinical criteria, CSW was regarded as a misnomer of SIADH and considered nonexistent or rare.

The overlapping clinical and laboratory characteristics have largely perpetuated the diagnostic and therapeutic dilemma of restricting water in SIADH, or administering salt and water in RSW. Both present with normal adrenal and thyroid function, hyponatremia, hypouricemia, concentrated urine with UNa usually >20 mmol/l, and FEurate $>10\%$.

Euvolemia in SIADH and ECV depletion in RSW are the only variables that differentiate SIADH from RSW on first encounter, but clinical assessment of ECV is inaccurate.[6] Treatment for RSW, however, can be initiated if FEphosphate is >20% on first encounter.[2] Moreover, exceptions and misconceptions have fueled this controversy, although it can be concluded that RSW is a clinical entity that is more common than is perceived and must now be considered in those without cerebral disease.[1,2]

VOLUME STUDIES

The difficulty to assess ECV accurately and adherence to the notion that RSW is a misnomer of SIADH are major reasons for this longstanding diagnostic dilemma. Accurate determinations of ECV should, therefore, resolve this dilemma. Determination of ECV by radioisotope dilution is the gold standard, which correlates poorly with concomitant central venous pressure (CVP) measurements, suggesting that CVP is an unreliable determinant of ECV.[7] Nelson *et al.* measured blood volume by ^{51}Cr-tagged red cells and ^{131}I-tagged albumin in 12 hyponatremic neurosurgical patients as compared with that in 6 control patients. Of the 10 patients with decreased blood volume, 8 had subarachnoid hemorrhage (SAH) and 2 had increased blood volume, suggesting that 10 had RSW and 2 SIADH.[8] The UNa ranged from 41 to 203 mmol/l.[8] Wijdicks *et al.* measured plasma volume by ^{131}I-tagged albumin in 21 patients on the first day of admission within 48 h after SAH and on the sixth day after SAH. They compared differences between both the measurements to determine ECV while receiving at least 1500 ml of fluid daily and comparable sodium intake. Of the nine hyponatremic patients, plasma volume decreased by 10–20% in six, <10% in two, and increased by 4% in one.[9] Interestingly, in 12 normonatremic patients, plasma volume decreased by >10% in 5, <10% in 3, and increased by >5% in 4. Moreover, all 8 hyponatremic patients and 10 of 12 normonatremic patients with decreased plasma volume were in negative sodium balance.[9] This study concurs with Nelson's study and shows that RSW can occur without hyponatremia.[9] In a study of hyponatremic patients with diverse neurosurgical diseases meeting criteria for SIADH, Sivakumar *et al.* found hypovolemia in 17 of 18 hyponatremic patients using ^{51}Cr-tagged red cells. All 18 patients had decreased CVPs.[10] UNa ranged from 43 to 210 mmol/l and all 18 patients corrected their hyponatremia within 72 h after initiating saline therapy, which was consistent with RSW and not SIADH.[1,2,10] In a retrospective study of 319 patients with SAH, Sherlock *et al.* found 179 hyponatremic patients meeting the criteria for SIADH and CSW. They found that 69.2% had SIADH, 6.5% CSW, and 4.8% had combined SIADH and CSW. ECV was determined by CVP measurements, presence of hypotension, and undefined parameters.[11] This report suffers by its retrospective design, paucity of data to support their diagnoses, and reliance on CVP measurements that are poor determinants of ECV.[7] Moreover, the combination of SIADH and CSW in 4.8% of patients lacked supportive data to justify such a mutually exclusive diagnostic combination. In total, 10 patients with AIDS with saline-responsive postural hypotension were selectively studied. All the patients had CVP of 0 cm water, increased renin and aldosterone, hyponatremia, hypouricemia, elevated FEurate, and UNa >40 mmol/l, which collectively support the diagnosis of RSW.[6] Overall, these volume studies support the notion that RSW not only exists but is more common than SIADH in neurosurgical patients.

PATHOPHYSIOLOGY OF RSW AND SIADH

In RSW, the initiating defect in renal sodium transport leads to ECV depletion and multiple compensatory changes. At the onset, sodium excretion exceeds sodium input to decrease ECV, but as compensatory hemodynamic and neurohumoral factors come into play, the patient enters an equilibrated state where sodium input matches output. As in our well-documented case of RSW, UNa can thus be as low as 6 mmol/l when sodium intake is low.[1] The final ECV depends on the extent of the renal sodium transport defect and sodium input. The reduced effective arteriolar volume activates baroreceptors that increase ADH secretion and increase water conservation. As insensible fluid losses are hypotonic, the tendency to develop hypernatremia must be overcome by adequate free water intake for hyponatremia to develop. In those with defective thirst as seen in the aged or demented, such as Alzheimer's disease (AD), RSW can occur without hyponatremia or even hypernatremia.[12] As will be discussed later, the presence of increased FEurate and lower serum urate in the absence of hyponatremia and demonstration of natriuretic activity in AD plasma suggest that RSW is common in those with moderate-to-severe AD.[12] In RSW the volume stimulus for ADH secretion overrides the usual inhibition by the coexisting plasma hypoosmolality. The ECV depletion stimulates aldosterone production, but the proximal sodium transport defect in RSW will maintain salt supply to the distal nephron when salt intake is adequate to yield normal cyclo-oxygenase 2 activity and renin production.[13]

The primary defect in SIADH is the euvolemic, inappropriate increase in plasma ADH levels. With adequate free water intake, the increase in water reabsorption induces hyponatremia, plasma hypoosmolality, and a small degree of volume expansion, which along with increased atrial natriuretic peptide levels, decrease plasma renin and aldosterone.[6] There is an initial salt wasting and water retention, often leading to an equilibrated state of vasopressin escape where sodium and water input matches output, possibly due to a reduction in V2 receptor and urea transporter 2.[2,6] The hypouricemia and increased FEurate occurring only during the period of hyponatremia have not been adequately explained but cannot be ascribed to V1 activity of ADH because ADH levels are increased even after correction of hyponatremia when FEurate returns to normal (Figure 1b).[6,14] Moreover, the induction of SIADH by desmopressin acetate, which lacks V1 activity, was associated

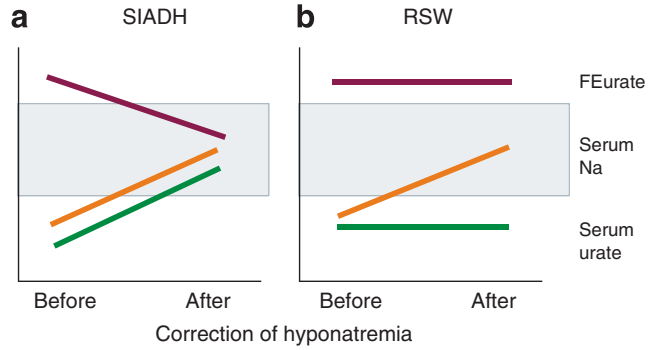

Figure 1 | Relationship between serum sodium, serum urate, and FEurate in SIADH and RSW. Relationship between serum sodium, serum urate, and FEurate in (**a**) inappropriate secretion of antidiuretic hormone (SIADH) and (**b**) renal salt wasting (RSW). Shaded areas represent normal values for each laboratory test. Hypouricemia and increased FEurate coexist with hyponatremia in both SIADH and RSW, but return to normal values with correction of hyponatremia in SIADH. In contrast, hypouricemia and increased FEurate persist after correction of hyponatremia in RSW. Serum sodium (orange), serum urate (green) and FEurate (red).

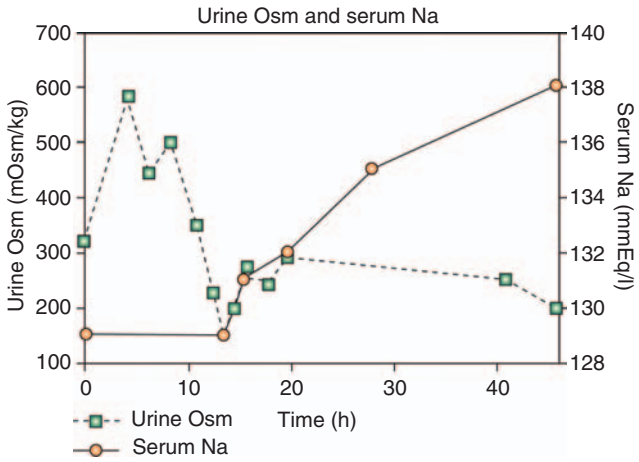

Figure 2 | Response of urine Osm and serum sodium concentration to saline infusion at 125 ml/h in hyponatremic patient with hip fracture without cerebral disease. Plasma antidiuretic hormone (ADH) was undetectable when urine Osm was 178 mOsm/kg water. Patient had 7.1% reduction in blood volume, increased plasma renin and aldosterone, and persistent hypouricemia and increased FEurate after correction of hyponatremia. Note prompt correction of hyponatremia after inhibition of ADH secretion and generation of dilute urine to increase free-water excretion.[1]

with an increase in FEurate.[15] ECV expansion as with saline is known to have a meager effect on FEurate but not to the extent seen in SIADH.[14]

VALUE OF FEurate OVER HYPOURICEMIA

Beck[16] proposed that the coexistence of hyponatremia and hypouricemia, defined as serum urate $\leqslant$4 mg per 100 ml, differentiated SIADH from most other causes of hyponatremia. The hypouricemia was largely due to increased FEurate. Interestingly, the hypouricemia and increased FEurate corrected after correction of the hyponatremia.[16] This relationship between sodium and urate has been observed by others in SIADH (Figure 1a).[14,16,17] We used this relationship between serum sodium, and serum urate and FEurate to differentiate SIADH from a group of patients whose hypouricemia and increased FEurate persisted after correction of their hyponatremia (Figure 1b).[6,14] One hyponatremic patient with bronchogenic carcinoma, normal CT scan of brain, and normal neurological examination, became profoundly volume-depleted during water restriction for an erroneous diagnosis of SIADH with postural hypotension, postural tachycardia, dry mucous membranes, flat neck veins, tenting of skin, and staggered gait, drooping of eyes, somnolence, and slurred speech on standing.[18] After his serum sodium increased to 138 mmol/l, his hypouricemia and increased FEurate persisted.[18] This and two other patients without cerebral disease prompted our concern that cerebral disease was not an invariable association in RSW.[18]

Increased FEurate with or without hyponatremia or hypouricemia was also noted in AIDS, as noted above, and all but two hyponatremic patients with diverse neurosurgical diseases and AD.[6,14] The persistence of hypouricemia and increased FEurate after correction of hyponatremia or in association with a normal serum sodium was inconsistent with SIADH and in our view represented a group with RSW (Figure 1b).[1,2,6,14] The persistent hypouricemia and increased FEurate that we reported in two patients with indisputable evidence of RSW supported our earlier proposal that this combination was a feature of RSW and that RSW can occur in patients without cerebral disease.[1,2] One had a hip fracture and the other pneumonia. Both were treated for an erroneous diagnosis of SIADH with fluid restriction, which induced anorexia and low sodium intake to account for the UNa of 6 mmol/l in the patient with a hip fracture.[1] She was initially thought to be a hypovolemic patient with normal kidneys, but the serum urate of 3.4 mg per 100 ml and FEurate of 29.6% were more consistent with either SIADH or RSW.[1,5] The 7.1% reduction in blood volume, increased plasma renin and aldosterone levels, and persistence of hypouricemia and increased FEurate after correction of hyponatremia were collectively diagnostic of RSW.[1] This case illustrates how a low sodium intake can result in low UNa in RSW, as sodium output reflects input when in an equilibrated state. In both cases without cerebral disease, saline removed the volume stimulus for ADH secretion and permitted the coexisting plasma hypoosmolality to inhibit ADH secretion, generate free water excretion, and correct the hyponatremia within 48 h (Figure 2).[1,2] Plasma ADH was undetectable when the urine was dilute in the patient with the hip fracture, a finding that illustrates the 'appropriateness' of ADH secretion in RSW.[1] The two cases of RSW strengthened our previous proposal that an increased FEurate in the absence of hyponatremia is a marker for RSW and support the applicability of our rat infusion studies to RSW (Figure 1b).[6,14] Finally, the baseline FEphosphate of 23% (normal $<$20%) in one patient is consistent with RSW, as FEphosphate was not present in the two patients with SIADH or reported in SIADH, and is a

clue to infuse saline when present at baseline.[2] The increase in FEurate, occasional increase in FEphosphate, and increased FElithium in our rat infusion studies all favor the proximal tubule as the major site of defective solute transport in RSW.[1,2,14]

ABSENCE OF PRERENAL AZOTEMIA IN RSW

The BUN to creatinine ratio normally expected in prerenal azotemia is often absent and does not differentiate RSW from SIADH. In our well-documented cases of RSW and SIADH, we were unable to show an increase in BUN to creatinine ratio in RSW as compared with SIADH, being 14 and 20 to 1 in RSW and 15.7 and 23.3 to 1 in SIADH.[8,9] This is an important issue to clarify with actual data because it focuses on a fundamental physiological abnormality in RSW that differs from those with ECV depletion and normal kidney function. The intact proximal tubule responds to ECV depletion by increasing reabsorption of urea and other solutes over a nonreabsorbable creatinine to increase the BUN to creatinine ratio in prerenal azotemia. The increases in FEurate, occasional FEphosphate and in our rat studies, FElithium, support our assertion that the proximal tubule is the major site of defective solute transport in RSW. The reduction in sodium and water reabsorption in the proximal tubule reduces the transtubular urea gradient to decrease passive urea reabsorption to prevent the disproportionate increase in BUN over creatinine. The renal response to ECV depletion in RSW, therefore, cannot be equated to those with ECV depletion and normal kidney function.

DIFFERENTIATING RSW FROM SIADH

Determination of ECV by radioisotopic techniques in neurosurgical patients suggests that RSW, especially those with SAH, is more common than SIADH in this population, but its overall prevalence is yet to be determined. This can be ascribed to several factors: consideration of RSW enters the differential only in hyponatremic patients or those with cerebral disease; patients who are normonatremic and without cerebral disease are being overlooked; and hyponatremia occurs less frequently in neurosurgical units because isotonic saline is the fluid of choice.[19] Saline is the treatment of choice because fluid restriction in neurosurgical units, especially those with SAH, increases morbidity and mortality.[19] We and others have encountered instances where fluid restriction for an erroneous diagnosis of SIADH led to clinical deterioration of the patient with RSW.[1,15] The combination of the difficulty to differentiate RSW from SIADH, and occurrence of RSW with and without cerebral disease or hyponatremia contribute to the diagnostic and therapeutic dilemma.

Although differentiating RSW from SIADH on first encounter can be made only by differences in ECV and by an occasional increase in FEphosphate $>20\%$, there are differences that can contribute to making the proper diagnosis and treatment plan. An increase in FEphosphate has been reported in RSW but not in SIADH.[2] FEphosphate should be determined before administering saline. We have shown by clearance and micropuncture studies that saline or mannitol can promptly increase FEphosphate by acutely decreasing serum calcium and magnesium to stimulate parathyroid hormone secretion.[20] We are uncertain what the FEphosphate should be during variable degrees of volume depletion and normal kidney function. The increase in baseline plasma renin and aldosterone levels in RSW can differentiate RSW from the usually depressed levels found in SIADH,[1,2] Plasma renin, however, can be normal in RSW if the patient is ingesting sufficient amounts of salt (Table 1).[2] The defect in proximal salt transport maintains an adequate distal salt load to blunt cyclo-oxygenase 2 and renin production.[19]

Table 1 | Differentiation of SIADH from RSW

	RSW	SIADH
ECV	↓	N-↑
UNa	N-↑	N-↑
Renin	± ↑	± ↓
Aldosterone	↑	± ↓
Serum urate	↓-↓	↓-N
FEurate	↑↑	↑-N
FEphosphate	± ↑	N

ECV, extracellular volume; RSW, renal salt wasting; SIADH, secretion of antidiuretic hormone; UNa, urinary sodium concentration.
Table comparing laboratory expectations for RSW and SIADH. UNa can be normal or often >20 mmol/l; serum urate and FEurate are increased during hyponatremia in both RSW and SIADH but differ when serum is normal. Serum urate and FEurate remain abnormal in RSW and normalize in SIADH when serum sodium is normal.

NATRIURETIC FACTOR IN RSW

The persistence of hypouricemia and increased FEurate in the absence of hyponatremia in RSW affords greater credibility to our earlier rat clearance studies in which we infused the plasma of largely nonhyponatremic neurosurgical and AD patients with increased FEurates.[6,12,14] When compared with plasma from age- and gender-matched controls, there were significant increases in both FElithium and FENa.[6,12,14] As lithium is reabsorbed on a one-to-one basis with sodium predominantly in the proximal tubule, the increase in FElithium from 24 to 36.6% and from 27.2 to 41.7% in rats exposed to neurosurgical and AD plasma, respectively, reflects the reduction in proximal tubule sodium transport and large distal load of sodium.[6,12,14] The relatively modest increase in FENa from 0.29 to 0.59% and 0.33 to 0.63% in rats exposed to neurosurgical and AD plasma, respectively, suggests significant compensatory increase in distal sodium reabsorption, although a mild inhibition of distal sodium transport by the natriuretic factor might also be present.[6,12,14] These results support our clinical impression that the proximal tubule is the major site of abnormal solute transport in RSW. As urate and phosphate, like lithium, are exclusively or predominantly transported in the proximal tubule, the increased FEurate and occasional FEphosphate in our patients supports the findings in our rat studies, that the proximal tubule is the major site of solute transport abnormality in RSW. Future studies must test whether the natriuretic factor in RSW affects one or more of the transporters for sodium, urate, phosphate, and urea.

Atrial/brain natriuretic peptides, including urodilatin, have been implicated as possible causes of RSW, but their contribution to RSW is not supported by their modest effect on sodium and other solute transport. These peptides are vasodilators that increase sodium excretion by increasing glomerular filtration rates and a meager effect on distal sodium transport.[21] The administration of atrial natriuretic peptide in normal humans had no effect on lithium excretion rates. The plasma from our neurosurgical and AD patients failed to decrease blood pressure or increase GFR, and the low-normal atrial natriuretic peptide of 35 pg/ml in our hip fracture patient makes it highly unlikely that atrial/brain natriuretic peptides or urodilatin contribute to the salt wasting in RSW.[6,12,14]

CHANGE CSW TO RSW

As discussed above, RSW is more common than SIADH in neurosurgical patients and with the recent reports of RSW occurring in patients without clinical cerebral disease, we must expand our differential to include RSW in patients without cerebral disease.[1,2] Both cases of RSW without cerebral disease were treated by water restriction for an erroneous diagnosis of SIADH.[1,2] Fluid restriction in RSW can lead to variable clinical manifestations depending on the severity of the sodium transport defect and ECV depletion.[1,6] In our present state of understanding these two disorders, it would be interesting to query how many patients with RSW with or without cerebral disease are being fluid restricted for an erroneous diagnosis of SIADH. The extent of their clinical deterioration may depend on the severity of their underlying sodium transport defect and reduced fluid intake, and not on deterioration of their underlying disease. It is time to discard the outmoded, misleading, and inappropriate term, CSW, in favor of a more inclusive RSW. This change in designation, however, will have limited utility unless we can identify those who are likely to have RSW and improve our ability to differentiate RSW from SIADH on first encounter. The combination of diametrically opposing treatment goals and awareness that RSW is a common disorder occurring without hyponatremia or cerebral disease should hasten our pursuit to resolve the diagnostic and therapeutic dilemma, and improve clinical outcomes.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

The authors would like to acknowledge funding from the Winthrop-University Hospital Special Fund for Biomedical Research.

REFERENCES

1. Maesaka JK, Miyawaki N, Palaia T *et al.* Renal salt wasting without cerebral disease: value of determining urate in hyponatremia. *Kidney Int* 2007; **71**: 822–826.
2. Bitew S, Imbriano L, Miyawaki N *et al.* More on renal salt wasting without cerebral disease, response to saline infusion. *Clin J Amer Soc Neph* 2009; **4**: 309–315.
3. Schwartz WB, Bennett W, Curelop S. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. *Am J Med* 1957; **23**: 529–542.
4. Peters JP, Welt LG, Sims EAH *et al.* A salt-wasting syndrome associated with cerebral disease. *Trans Assoc Am Physicians* 1950; **63**: 57–64.
5. Abuelo JG. Normotensive ischemic acute renal failure. *NEJM* 2007; **357**: 797–805.
6. Maesaka JK, Gupta S, Fishbane S. Cerebral salt wasting syndrome: does it exist? *Nephron* 1999; **82**: 100–109.
7. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest* 2008; **134**: 172–178.
8. Nelson PB, Seif SM, Maroon JC *et al.* Hyponatremia in intracranial disease: perhaps not the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *J Neurosurg* 1981; **55**: 938–941.
9. Wijdicks EFM, Vermeulen M, ten Haaf JA *et al.* Volume depletion and natriuresis in patients with a ruptured intracranial aneurysm. *Ann Neurol* 1985; **18**: 211–216.
10. Sivakumar V, Rajshekhar V, Chandy MJ. Management of neurosurgical patient with hyponatremia and natriuresis. *Neurosurgery* 1994; **43**: 269–274.
11. Sherlock M, O'Sullivan E, Agha A *et al.* The incidence and pathophysiology of hyponatremia in subarachnoid hemorrhage. *Clin Endocrin* 2006; **64**: 250–254.
12. Maesaka JK, Wolf-Klein G, Piccione JM *et al.* Hyporuicemia, abnormal renal tubular urate transport, and plasma natriuretic factor(s) in patients with Alzheimer's disease. *J Am Geriatr Soc* 1993; **41**: 501–506.
13. Harris RC, Zhang MZ, Cheng HF. Cyclooxygenase-2 and the renin-angiotensin system. *Acta Physiol Scand* 2004; **181**: 543–547.
14. Maesaka JK, Fishbane S. Regulation of renal urate excretion: a critical review. *Am J Kidney Dis* 1998; **32**: 917–933.
15. Boer WH, Koomans HA, Dorhout Mees EJ. Lithium clearance during the paradoxical natriuresis of hypotonic expansion in man. *Kidney Int* 1987; **32**: 376–381.
16. Beck LH. Hypouricemia in the syndrome of inappropriate secretion of antidiuretic hormone. *N Engl J Med* 1979; **301**: 528–530.
17. Sonnenblick M, Rosin A. Increased uric acid clearance in the syndrome of inappropriate secretion of antidiuretic hormone. *Isr J Med Sci* 1988; **24**: 20–23.
18. Maesaka JK, Batuman V, Yudd M *et al.* Hyponatremia and hypouricemia: differentiation from the syndrome of inappropriate secretion of antidiuretic hormone. *Clin Nephrol* 1990; **33**: 174–178.
19. Wijdick EFM, Vermeulen M, Hijdra A *et al.* Hyponatremia and cerebral infarction in patients with ruptured intracranial aneurysm: is fluid restriction harmful. *Ann Neurol* 1985; **17**: 137–140.
20. Maesaka JK, Levitt MF, Abramson RG. Effect of saline infusion on phosphate transport in intact and thyroparathyroidectomized rats. *Am J Physiol* 1973; **225**: 1421–1429.
21. Cogan ME. Atrial natriuretic factor can increase renal solute excretion primarily by raising glomerular filtration. *Am J Physiol* 1986; **250**: F710–F714.