Letter and Reply

Hyponatraemia in a neurosurgical patient

Sir,

In his report on *Hyponatraemia in a neurosurgical patient* [1] Palmer describes several unresolved issues—termed ‘cerebral salt wasting’ by some—in this particular setting. The article by Palmer is very interesting. In my opinion it also raises a number of questions.

(i) Why does the case report omit basically all those data that would be required to support the diagnosis of a decreased effective arterial blood volume (EABV)? Such data might have been: blood urea concentration, complete arterial blood gases, plasma renin, plasma and 24 h urinary aldosterone, ANP, pulmonary wedge pressure. Why are we not given sequential data on how the disturbances reported evolved during the days preceding the state reported and also later on when the disturbance was obviously resolved? Why are the infusion rate of hypertonic fluids, the oral intake of hypertonic fluids and the infusion rate of NaCl-solutions not reported?

(ii) The case description probably shows a patient with a cerebral event who also fulfills criteria for—at least functional—adrenal insufficiency: hyperkalaemia, hyponatraemia, probable metabolic acidosis, high urinary sodium excretion in the presence of inappropriately low urinary potassium excretion, hypotension and pathologic orthostatic changes on day 10. Reportedly, ‘tests of … adrenal function were normal’. Measurements of adrenal function are notoriously variable; even if such measurements had been taken repeatedly and carefully in this case there is still a distinct possibility that this chronic alcoholic had relative (functional) adrenal insufficiency primarily involving mineralocorticoids on day 10. Such functional adrenal insufficiency could have been related to stress at this time necessitating ‘elevated’ instead of ‘normal’ adrenal hormones for appropriate compensation. I therefore suspect that adrenal function was not normal. Furthermore, the gross discrepancy between the urinary excretion of potassium versus sodium also is a strong indicator of mineralocorticoid insufficiency. Therefore, the case presented is probably not an example of cerebral salt wasting; instead it is highly likely that this man had functional adrenal insufficiency, leading to vasopressin stimulation. He was probably infused with hypertonic fluids at a high rate causing moderately severe hyponatraemia.

(iii) In Figure 1, an algorithm concerning the diagnosis of hyponatraemia is provided. The algorithm speaks about pseudo-hyponatraemia; however, this is nowadays a mute issue, because most hospitals measure the sodium concentration by ion-selective electrode. The proposed distinction between an ‘appropriately low’ and an ‘inappropriately high’ urinary osmolality looks nice on paper—but it is rather worthless in real life: (a) because of the phenomenon of ADH-escape, urinary osmolality can fall to less than 100 mOsm/kg in the presence of hyponatraemia in SIADH which would then probably cause a reader of Dr Palmer’s algorithm to put this patient into the categories of primary polydipsia, beer potomania syndrome; (b) many patients with a decreased EABV caused by an oedematous disorder will be on diuretics. This will lower their urinary osmolality often getting into the range of plasma isotonicity. Thus, there would be a danger that even these patients could be considered by some physicians to have ‘appropriately low’ urinary osmolality according to Dr Palmer’s table. In the table, the term primary polydipsia is misleading; instead it would have been better to talk about ‘psychogenic (secondary) polydipsia’ according to the literature.

(iv) I am unaware of any publications having shown that infusions of either ANP or BNP caused hyponatraemia.

(v) Why did Dr Palmer omit to mention that a water restriction would have been indicated in the treatment of the hyponatraemia of the present case?

In summary, in the case presented so-called cerebral salt wasting was probably identical to functional adrenal insufficiency with hyponatraemia; the latter was probably precipitated by inappropriately high infusion rates of hypertonic fluid. Since Dr Palmer does not suggest any convincing characteristics (clinical science, laboratory tests, circulatory measurements) for CSW, I wonder if alleged cerebral salt wasting might sometimes conform to the pattern outlined here. We know from kidney explantation in the brain-dead donor that this cerebral state is associated with multiple hormonal changes probably because of extreme cerebral stress. Neurosurgical patients are likely to have such stress also, however on a much smaller scale. Presumably this could suffice in some of them to bring about functional insufficiency of the adrenal gland. The high infusion rates of fluids often seen in some surgical units, including neurosurgical units, might then suffice to precipitate hyponatraemia from adrenal insufficiency. Before one searches for elusive hormones to explain elusive cerebral salt wasting, more physiological and known possibilities ought to be explored as indicated here.

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Reply

Sir,

The letter raises several issues regarding the recent review of cerebral salt wasting (CSW) published in the Continuing Nephrological Education series [1]. The author requests additional information regarding the volume status of the patient presented. In particular, the author requests values for the pulmonary capillary wedge pressure, and levels of atrial natriuretic hormone, plasma renin activity, and plasma and urinary aldosterone. As described in the paper, the patient’s physical examination at the time of development of hyponatraemia showed orthostatic changes in blood pressure and pulse. Although not mentioned in the report, the patient’s weight had declined as compared to the previous several days. These routine clinical findings clearly show the patient was volume depleted and obviate the need for more invasive procedures that carry risk or measurement of expensive tests...
that are only indirectly reflective of effective arterial blood volume (EABV). The importance and effectiveness of the physical examination in assessing volume status has recently been commented upon [2].

Prior to the development of hyponatraemia the patient was taking per os, and not receiving, intravenous fluids. Once the diagnosis of CSW was made he was treated with normal saline as the mainstay of therapy as opposed to free water restriction. The importance of distinguishing CSW from SIADH is of particular importance with regards to therapy. As detailed in the original paper, free water restriction as the sole therapy for a patient with CSW can result in an adverse outcome just as can administration of normal saline to a patient with SIADH [3]. It should be emphasized that the laboratory tests reported in the paper were obtained prior to the administration of intravenous fluids.

The author suggests that functional adrenal insufficiency may account for the electrolyte disturbances in the patient. Adrenal insufficiency is certainly worthy of consideration since this disorder can be associated with hyponatraemia, hypovolaemia, and increased urinary Na excretion. However, there are several reasons that make this diagnosis highly unlikely. First, functional adrenal insufficiency would become clinically apparent under conditions of greatest stress. The electrolyte abnormalities in this patient were not present upon admission when the patient was presumably under the greatest amount of stress. Rather, the abnormalities became apparent 10 days later when he was otherwise stable and undergoing rehabilitation. Second, other features typical of adrenal insufficiency were not present such as metabolic acidosis, hypoglycaemia, or eosinophilia. Third, a random cortisol level measured at the time of the work up was 18 µg/dl. At no time was the patient clinically unstable suggesting a state in which the glucocorticoid needs of the body were in excess of the synthetic capacity of the adrenal gland. Fourth, the serum uric acid concentration was low. In most cases of volume depletion to include adrenal insufficiency the serum uric acid is typically increased. By contrast, uric acid levels are often low in CSW despite the presence of volume depletion. While the precise mechanism by which this occurs is not known it may reflect decreased proximal reabsorption. Finally, the patient had no other known disease process present that would have made him at risk for adrenal insufficiency.

Although there is little reason to suggest that this patient had adrenal insufficiency, it is worth pointing out that patients with CSW typically have a blunted rise in serum aldosterone levels despite the presence of a decreased EABV. The relatively low level of circulating aldosterone accounts for the lack of renal potassium wasting and development of hypokalaemia despite the presence of increased distal Na delivery. It has been suggested that in CSW circulating levels of aldosterone are low as a result of decreased sympathetic outflow leading to decreased release of renin from the juxtaglomerular cells. In addition, increased atrial or brain natriuretic hormone levels in CSW could limit circulating aldosterone levels due to direct inhibitory effects on renin release as well as direct inhibition of aldosterone release within the zona glomerulosa cells of the adrenal gland.

The author raises several issues regarding the algorithm for the workup of the hyponatraemic patient. The author suggests that pseudohyponatraemia should no longer be an issue since most hospitals measure the serum Na by ion selective electrodes. Direct ion-specific electrodes assess Na activity rather than concentration and eliminate the phenomena of pseudohyponatraemia. In fact, pseudohyponatraemia remains an issue in the United States since most clinical laboratories measure the serum Na by indirect ion-specific electrodes, which determine the Na concentration rather than its activity [3]. This technique is preferred in instruments designed to perform multiple tests on large numbers of samples in a short period of time. In the setting of severe hypertriglyceridaemia or high concentration of a paraprotein the non-aqueous volume of plasma is markedly increased and results in lower concentration of Na in the total plasma. The activity of Na in the aqueous fraction of plasma as measured by the direct use of an ion-selective is normal under these conditions. The indirect ion-specific electrode as well as the older technique of flame photometry both include a dilution step prior to the analysis and thus measure the concentration of Na in the total plasma volume. As a result, these techniques are subject to pseudohyponatraemia in the appropriate clinical setting. Thus, pseudohyponatraemia has not been eliminated and clinicians need to be aware of the technique utilized by the clinical laboratory when evaluating a hyponatraemic patient with high serum lipids or protein values.

The author next questions the usefulness of the terms, appropriately low or inappropriately high osmolality, citing the condition of SIADH and suggesting that urine osmolality may fall to <100 mOsm/kg as a result of ADH-escape. ADH-escape refers to observations made in experimental models of SIADH where sustained administration of vasopressin and water results in free-water retention and progressive hyponatraemia for several days after which the urine becomes less concentrated. At this point, water excretion increases despite sustained administration of vasopressin, allowing water balance to be re-established and the serum Na to be stabilized at a steady, albeit decreased, level. In clinical conditions characterized by vasopressin-mediated water retention such as SIADH, cirrhosis, or congestive heart failure, renal escape from vasopressin-induced antiureauresis allows for a relatively stable level of hyponatraemia to be maintained despite continued water intake and continued presence of vasopressin. The mechanism by which this escape occurs is multifactorial and includes down regulation of the aquaporin-2 water channel [4], down regulation of vasopressin V2 receptor binding capacity [5], and antagonizing effects of atrial natriuretic peptide [6] and renal prostaglandins [7].

While these mechanisms limit the ability of circulating vasopressin to maximally concentrate the urine, ADH-escape is not so efficient that urine osmolality can be returned to values <100 mOsm/kg in the steady state. Were this to occur, then hyponatraemic patients with SIADH would demonstrate spontaneous correction of the serum sodium concentration even though circulating levels of ADH were still elevated. Rather, patients with SIADH are not able to maximally dilute the urine due to a persistent (albeit somewhat less) effect of ADH to concentrate the urine. The urine can be considered to be inappropriately concentrated since the urine osmolality is typically greater than 200 mOsm/kg. It should be emphasized that in the setting of hyponatraemia the appropriate response of the kidney should be to maximally dilute the urine to values less than 100 mOsm/kg.

There are two situations in which the urine osmolality may reach a value of <100 mOsm/kg in the setting of SIADH. The first situation is when an additional bolus of water is administered to a hyponatraemic SIADH subject who is already in water balance. In this setting, administration of a water load will result in a transient drop in urine osmolality. Once the water load is excreted and the patient is allowed to return to the previous level of water intake, the urine osmolality will rise to the previous steady state level. The
second situation is not the result of ADH escape but rather relates to a specific pattern of ADH release that has been described in patients with SIADH [8]. This pattern of release is similar to normal subjects, as ADH release correlates closely with plasma osmolality; however the osmotic threshold for ADH release is abnormally low. If these patients are made sufficiently hyponatraemic then ADH release is inhibited and the urine becomes maximally dilute. As the plasma osmolality returns to baseline then ADH levels increase and the urine becomes concentrated. This pattern of ADH release may correspond to patients previously described as having a 'reset osmostat'.

In these two situations the decline in urine osmolality is a transient phenomena. The clinical evaluation of SIADH patients typically occurs when such patients are in a steady state and in this setting the urine is not maximally dilute but rather is concentrated. Thus, measurement of the urine osmolality as a means to determine whether the urine is appropriately dilute or inappropriately concentrated not only makes sense on paper but is also quite useful in the clinical workup of the hyponatraemic patient.

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