Beyond semantics: Defining hyponatremia in secondary adrenal insufficiency

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Although the association of hyponatremia with hypopituitarism has been reported since the fifties, its pathophysiology remains a matter of debate. In primary adrenal failure, hyponatremia is closely related to the lack of mineralcorticoid action and, as a result, hyperkalemia and symptoms of volume depletion often develop. Conversely, the origin of hyponatremia occurring in patients with secondary adrenal insufficiency has not yet been completely clarified, even though some data give strength to the emerging role of inappropriate antidiuresis in these patients, who usually do not present with hypovolemia (1-6). Indeed, there is a substantial body of evidence that water retention due to impaired renal free water excretion, rather than renal sodium wasting, contributes to the pathogenesis of hyponatremia in hypopituitarism. What mechanism does this impaired renal water excretion share? Is it really an inappropriate antidiuresis? If so, should one consider hyponatremia accompanying hypopituitarism as a result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), as proposed by some authors? Therein lies the major question.

The beginning of this story is undoubtedly the definition of SIADH. In 1967, 10 yr after their classical paper characterizing SIADH, Barter and Schwartz defined the essential features of this clinical syndrome as well as the excluding criteria (7); together, these characteristics readily became the cornerstones for the diagnosis. Briefly, in the setting of euvolemia and in the absence of renal disease, adrenal failure, hypothyroidism, or hypotension, SIADH exhibits an inability to excrete a free water load in association with inappropriately concentrated urine and consequent hyponatremia, plasma hyposmolality, and natriuresis. It is worth noticing that each of the excluding conditions may also result in impaired water excretion and hyponatremia, despite different pathophysiology and therapy. On the basis of subsequent evidence, excluding conditions may also include nausea (8). SIADH is a volume-expanded state primarily due to an excessive AVP release resulting in increased renal water reabsorption and expansion of the extracellular fluid volume, with evidence of normal or slightly increased intravascular volume. Therefore, fluid restriction is the treatment of choice. Interestingly, at the time of the work by Barter and Schwartz, serum AVP levels could not be measured, but subsequent studies showed that SIADH is almost always associated with measurable serum levels of AVP, indicating insufficient suppression of AVP release despite plasma hyposmolality, since AVP secretion is usually suppressed when the plasma osmolality falls below 275 to 280 mOsm/kg (9).

The idea that AVP secretion is tonically inhibited by glucocorticoids was first suggested by animal and clinical studies in the sixties (10, 11), with subsequent confir- mations that glucocorticoid deficiency may be another important non-osmotic stimulus to AVP secretion in addition to more classical stimuli, such as hypotension, hypovolemia, and nausea (12). The quest to define the origin of hyponatremia in secondary adrenal failure culmin- ated in 1989, when Oelkers reported a retrospective study recruiting 5 inpatients that presented with symptomatic hyponatremia and hypopituitarism (2). The study unequivocally showed that hyponatremia developed in concert with inappropriately high plasma AVP levels and impaired dilution of the urine; furthermore, hydrocortisone replacement promptly corrected hyponatremia. In his conclusions, Oelkers stated that “ACTH deficiency may cause the syndrome of inappropriate secretion of antidiuretic hormone”. Actually, in his editorial accompanying Oelkers’ study, Robertson had a word of caution about such a conclusion, reminding us how other conditions, including postural hypotension, nausea, and hypoglycemia, may occur in patients with adrenal insufficiency and concur at least in part in stimulating...
AVP release as appropriate stimuli (13). Furthermore, Robertson also stressed a possible additional vasopressin-independent antiuretic effect of glucocorticoid deficiency, as indicated by the ability of adrenal failure to impair urine dilution and solute free water excretion in experimental models of diabetes insipidus, namely in conditions of AVP deficiency (14).

Over the last few years, other studies have addressed the issue. In particular, two reports, by Yatagai et al. (4) and one by Diederich et al. (5), shed new light on this controversial matter, the former providing further evidence that in patients with hyponatremia and hypopituitarism an increased AVP release develops despite plasma hyposmolality, thus leading to inappropriate antidiuresis, and the latter demonstrating in a large population that secondary adrenal insufficiency may really be a common overlooked cause of severe hyponatremia. Interestingly, both studies raised critical new questions with regard to the age in the pathophysiology of hyponatremia associated with hypopituitarism, suggesting that elderly patients are extremely inclined to develop severe hyponatremia. Analyzing a population of hyponatremic patients with hypopituitarism, Yatagai et al. showed that, for a given degree of plasma hyposmolality, subjects 65 yr of age or older had lower serum sodium levels and higher plasma AVP levels than younger subjects (4). This finding confirmed the natural tendency of normal elderly subjects to have a lowered threshold triggering AVP release (15). Considering this background, we should also be aware that the median age of patients (59 to 83 yr old) reported in 1989 by Oelkers was 72 yr (2), a fact that was probably disregarded at that time. Thus far, in addition to secondary adrenal failure, aging is certainly another important factor to be considered in the pathogenesis of hyponatremia in patients with hypopituitarism. Finally, it was Olchovsky et al. who drew attention to the topic in a recent issue of the Journal of Endocrinological Investigation (6), confirming the role of aging in their analysis of 10 patients with symptomatic hyponatremia as a presenting sign of hypothalamic-pituitary disease. On the basis of biochemical parameters of electrolyte imbalance and the prompt correction of hyponatremia by glucocorticoid replacement, they defined hyponatremia occurring in hypopituitarism as “a SIADH-like glucocorticosteroid responsive condition”. Thus, the first major question reported above arises again.

In summary, what should the clinician conclude from the literature on the topic? First of all, the sobering finding of increased AVP release despite plasma hyposmolality must not be ignored. The main mechanism responsible for this inappropriate antidiuresis is probably glucocorticoid deficiency, which constitutes a non-osmotic stimulus to AVP release. In fact, patients given glucocorticoid replacement readily corrected hyponatremia. Another important finding that could change our understanding of this disorder comes from recent studies showing that elderly patients with hypopituitarism are more liable to develop hyponatremia than younger ones. Even our own experience supports this view. The reason why this phenomenon occurs is unclear. One possibility is a decrease of the threshold triggering AVP secretion.

Second, besides inappropriate antidiuresis, other factors have to be considered. Notably, a number of “classical” non-osmotic stimuli to AVP release, such as hypotension and nausea, may act in concert with glucocorticoid deficiency in patients with secondary adrenal insufficiency. Third, glucocorticoid deficiency per se could also modify the renal sensitivity to AVP, amplifying the inability to excrete a free water load. It is well known that the antidiuretic effect of AVP is mediated by its binding to the V2 vasopressin receptor on the basolateral membrane of the collecting-duct cells of the nephron. Ligand binding promotes a series of intracellular events leading to the fusion of cytoplasmic vesicles containing aquaporin-2 water-channel proteins with the apical membrane, which becomes water-permeable. The transient water-permeable state of the apical membrane permits water, driven by the osmotic gradient of sodium, to enter the cells and then go to the interstitium through the basolateral membrane, thus inducing antidiuresis. Given recent data demonstrating a vasopressin-dependent upregulation of aquaporin-2 gene expression in glucocorticoid-deficient rats (16), one could also speculate together with Chanson (17) that, for a given AVP level, excretion of free water by the kidney may be further reduced in patients with hypocortisolism.

Finally, significant lower plasma bicarbonate and aldosterone levels have been recently found in patients with hyponatremia related to ACTH deficiency in comparison with patients with classical SIADH (due to organic brain disease, oat cell carcinoma, carbamazepine, pneumonia, or larynx carcinoma), providing new evidence in favor of the hypothesis that a real difference in the pathophysiology of these two conditions may exist (18). Interestingly, patients with classical SIADH had normal plasma aldosterone levels coupled with low plasma renin activity despite mild volume expansion, thus disclosing a kind of relative hyperaldosteronism, which was not shown in patients with hyponatremia related to ACTH deficiency (18). However, uncertainty persists about the issue, since it has not yet been completely clarified whether low serum bicarbonate found in patients with hyponatremia related to ACTH deficiency may reflect compensated respiratory alkalosis (occurring in absence of relative hyperaldosteronism), metabolic acidosis (due to accumulation of hydrogen ions as a consequence of relative hypoaldosteronism caused by cortisol deficiency), or a mixed acid-base disturbance (respiratory alkalosis accompanying chronic hyponatremia irrespective of its pathogenesis and metabolic acidosis related to hypocortisolism).