Severe hyponatremia as a frequent revealing sign of hypopituitarism after 60 years of age

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Hyponatremia is a common electrolyte disorder often attributed to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (1). This syndrome is characterized by hyponatremia secondary to increased total body water resulting from impaired renal free-water excretion. Despite their hypo-osmolality, patients with SIADH fail to suppress arginine vasopressin (AVP) secretion even when plasma osmolality falls below the normal osmotic threshold triggering AVP secretion. Bartter and Schwartz, in their initial description of the syndrome (2), recommended that adrenal insufficiency be ruled out before diagnosing SIADH. Hyponatremia is a classical electrolyte disorder in decompensated Addison’s disease, leading to a search for adrenal failure when hyponatremia is associated with hyperkalemia and hypovolemia. In primary adrenal failure hyponatremia is explained, at least in part, by the absence of mineralocorticoid secretion, leading to urinary sodium wasting. In contrast, secondary adrenal failure is far more rarely sought in the patient with isolated euvoletic hyponatremia (which has a very different mechanism; see below). This frequently leads to misdiagnosis, especially as these patients usually complain only of unexplained fatigue, loss of energy, nausea or vomiting, or present with confusion or coma. Many physicians probably consider hyponatremia to be a ‘normal’ consequence of aging, and therefore conduct only minimal investigations (and rarely a cortisol assay). This can markedly delay the diagnosis, as is nicely illustrated by the study of Diederich et al. which appears in the present issue of the Journal (3). Patients with hyponatremia had been admitted to other hospitals between 1 and 4 times before being referred to the authors’ university hospital in Berlin, where their hypopituitarism was finally diagnosed. Moreover, hypopituitarism was undiagnosed before the hyponatremic episode in 89% of cases, and previous hyponatremic episodes were documented in 43% of patients. It might, therefore, have been more instructive to publish this article in a non specialized journal targeting GPs, emergency room physicians, or specialists in internal medicine, so as to teach them not to forget hypopituitarism when facing a patient with hyponatremia!

However, the authors provide some very interesting clinical information for endocrinologists. In particular, they confirm that elderly patients are particularly prone to this hydroelectrolytic complication of hypopituitarism. Indeed, only 3 of 28 patients were less than 60 years of age, and their mean age (68 years) was about 10 years lower than that of patients with other causes of SIADH admitted to their institution. Ishikawa et al. have previously reported that 40% of patients with hyponatremia aged 65 years or older had pituitary–adrenal dysfunction (4). This propensity of elderly patients with secondary adrenal failure to develop hyponatremia has also been studied by the same group (4, 5), and some of their results appeared in a very recent issue of the Journal (5). Patients with hyponatremia and hypopituitarism have inappropriate antidiuresis, related not only to the non suppressible AVP release (despite hypo-osmolality) but also, probably, to a direct renal water excretion defect. Plasma AVP levels are ‘normal’ or increased despite hypo-osmolality, in most patients with hyponatremia and hypopituitarism, reflecting increased AVP release and, when elevated at baseline, fall in response to hydrocortisone (3). Interestingly, in elderly patients (65 years or older), serum sodium levels are lower and plasma AVP levels higher (for a given degree of plasma hypo-osmolality) than in younger patients with secondary adrenal failure (5). Such a change in the threshold triggering AVP secretion has previously been described in ‘normal’ elderly subjects (6). The high prevalence of hyponatremia among elderly people with secondary adrenal failure is thus probably related to a combination of two factors known to increase AVP secretion, namely aging and hypocortisolism. Other factors also probably contribute to hyponatremia in these patients. Nausea-vomiting and hypoglycemia (related to both adrenocorticotropic/cortisol and growth hormone/insulin-like growth factor-I deficiency) are non osmotic stimuli of AVP release. Hypopituitarism, and particularly hypocortisolism, may also specifically alter renal sensitivity to AVP. As suggested by aquaporin-2 water channel up-regulation in glucocorticoid-deficient rats (7), it is likely that, for a given AVP level, patients with hypocortisolism excrete less free water, further contributing to the onset of hyponatremia. This probably also explains why a subset of patients with hypopituitarism have hyponatremia despite low plasma AVP levels (3). In contrast, the contribution of hypothyroidism is probably minimal: hypo-osmolar status recovers as soon as cortisol...
deficiency is corrected, long before thyroid deficiency is 
adequately substituted (3).

As the general population ages it is no longer rare to 
diagnose pituitary adenomas in the elderly. But the pre-
senting signs of these tumors are probably different in 
this age range. Pituitary incidentalomas may be one 
such situation (8) and hyponatremia another. Sym-
toms of hypopituitarism such as fatigue and loss of 
energy are non specific (9) and may be considered ‘normal’ in the elderly patient. In addition, gonadal 
dysfunction is unhelpful in this age group, particularly 
in women. As a result, hypopituitarism often goes 
undiagnosed. As recommended by Diederich et al. in 
their conclusion (3), ‘the best means to detect the 
patient with hypopituitarism among others with 
severe hyponatremia is a high level of clinical suspi-
cion’. This is particularly true for elderly patients.

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