INVITED COMMENTARY

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

Philippe Chanson

Endocrinology and Reproductive Diseases, Bicêtre Hospital and University Paris XI, Le Kremlin-Bicêtre, France

(Correspondence should be addressed to P Chanson, Service d'Endocrinologie, CHU Bicêtre, 78 rue du Maréchal Leclerc, F-94275 Le Kremlin-Bicêtre, France; Email: philippe.chanson@bct.ap-hop-paris.fr)

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 their 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 have 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 adrenocorticotropin/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 presenting signs of these tumors are probably different in this age range. Pituitary incidentalomas may be one such situation (8) and hyponatremia another. Symptoms 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 suspicion'. This is particularly true for elderly patients.

References

- 1 Adroge HJ & Madias NE. Hyponatremia. *New England Journal of Medicine* 2000 **342** 1581–1589.
- 2 Bartter FC & Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. *American Journal of Medicine* 1967 **42** 790–806.
- 3 Diederich S, Franzen N-F, Bähr V & Oelkers W. Severe hyponatremia due to hypopituitarism with adrenal insufficiency: report on 28 cases. *European Journal of Endocrinology* 2003 **6** 609–617.
- 4 Ishikawa S, Saito T, Fukagawa A, Higashiyama M, Nakamura T, Kusaka I *et al.* Close association of urinary excretion of aquaporin-2 with appropriate and inappropriate arginine vasopressin-dependent antidiuresis in hyponatremia in elderly subjects. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 1665–1671.
- 5 Yatagai T, Kusaka I, Nakamura T, Nagasaka S, Honda K, Ishibashi S *et al.* Close association of severe hyponatremia with exaggerated release of arginine vasopressin in elderly subjects with secondary adrenal insufficiency. *European Journal of Endocrinology* 2003 **148** 221–226.
- 6 Goldstein CS, Braunstein S & Goldfarb S. Idiopathic syndrome of inappropriate antidiuretic hormone secretion possibly related to advanced age. *Annals of Internal Medicine* 1983 **99** 185–188.
- 7 Saito T, Ishikawa SE, Ando F, Higashiyama M, Nagasaka S & Sasaki S. Vasopressin-dependent upregulation of aquaporin-2 gene expression in glucocorticoid-deficient rats. *American Journal of Physiology - Renal Physiology* 2000 **279** F502–F508.
- 8 Chanson P & Young J. Pituitary incidentalomas. *Endocrinologist* 2003 **13** 124–126.
- 9 Lamberts SW, de Herder WW & van der Lely AJ. Pituitary insufficiency. *Lancet* 1998 **352** 127–134.

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