

Does ‘asymptomatic hyponatremia’ exist?

Hyponatremia is characterized by the equilibration of water across cell membranes into cells, which leads to cell swelling. This phenomenon has been extensively studied experimentally in the brain (Verbalis, J. G. & Gullans, S. R. *Brain Res.* **567**, 274–282; 1991). Swollen brain cells react to hyponatremic conditions by decreasing their volume over approximately 48 h by the extrusion of potassium, sodium, chloride, and organic osmolytes. Among the extruded organic osmolytes are glutamate, taurine, myo-inositol, glutamine, and creatine. Although it must be emphasized that glutamergic activity is pivotal for brain function, the process by which brain cells adapt to hyponatremia is nevertheless extremely important, since the skull limits brain swelling to only 8% before brain-stem herniation occurs. However, the diminished intracellular osmolyte content associated with chronic hyponatremia predisposes the adapted brain to osmotic demyelination. Moreover, brain damage and even death can occur if chronic hyponatremia is corrected too rapidly (that is, with increases of sodium greater than 10–12 mmol/l over 24 h).

The term ‘asymptomatic hyponatremia’ is frequently used in clinical settings. This terminology may be used because the symptoms of mild or moderate hyponatremia (<125–135 mmol/l), which include lethargy, restlessness, disorientation, headache, nausea and vomiting, muscle cramps, and depressed neural reflexes, are rather non-descript. However, complications associated with hyponatremia that is more severe (<125 mmol/l) and evolves rapidly (over hours), can include seizures, coma, and cardiopulmonary arrest, and can be life threatening.

Of interest with regard to the concept of ‘asymptomatic hyponatremia’ is a study of patients with hip fracture who were treated at an emergency medical center. These patients had a 67-fold higher risk (as assessed by the adjusted odds ratio) of being hyponatremic than being normonatremic (Renneboog, B. *et al. Am. J. Med.* **119**, 71.e1–71.e8; 2006). The authors of this study also showed that ‘asymptomatic hyponatremia’ was associated with gait disturbances and decreased reaction time, which

mimicked alcohol excess. In another study, mild hyponatremia, defined as a mean serum sodium concentration of approximately 131 mmol/l, was associated with an increased risk of bone fracture (adjusted odds ratio of 4.16) in ambulatory elderly patients (Gankam Kengne, F. *et al. Q. J. Med.* **101**, 583–588; 2008). Moreover, the combined results of two identical randomized, double-blind, placebo-controlled studies of 448 patients with hyponatremia demonstrated that a significant rise in plasma sodium concentration with administration of a vasopressin V2 receptor antagonist over 30 days was

associated with a significant improvement in the mental component of the Medical Outcomes SF-12® survey of general health (Medical Outcomes Trust, Inc., Waltham, MA, USA) (Schrier, R. W. *et al. N. Engl. J. Med.* **355**, 2099–2112; 2006).

With the growing elderly population and increased recognition of subclinical, as well as clinical, dementia in elderly individuals, it is worth noting that hyponatremia has been reported in up to 30% of geriatric patients in nursing homes. Moreover, thiazide diuretics are still the recommended initial antihypertensive therapy for elderly patients, despite their known hyponatremic adverse effects, particularly in elderly women. Hyponatremia is also present in approximately 30% of depressed patients on selective serotonin reuptake inhibitors. In addition, hyponatremia is a major risk factor for mortality in patients with advanced heart failure and cirrhosis—clinical entities that are known to predispose patients to encephalopathy. The question for these populations, therefore, is how often should hyponatremia, even in patients with serum sodium concentrations within the range of 130–135 mmol/l, be considered to be ‘asymptomatic’? ‘Asymptomatic’ hypokalemia, which predisposes individuals to cardiac arrhythmias, is virtually always treated. When ‘asymptomatic hyponatremia’ should be treated is therefore an important clinical issue whether considering fluid restriction or treatment with furosemide or hypertonic saline, demeclocycline, or V2 receptor antagonists.

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“...how often should hyponatremia ... be considered to be ‘asymptomatic’?”

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Competing interests
R. W. Schrier declares an association with the following company: Otsuka Pharmaceuticals. See the article online for full details of the relationship.