Chronic hyponatraemia and risk of myelinolysis: why is it so difficult to control the change in plasma sodium?

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Acute hypotonic hyponatraemia is almost always caused by excess total body water — in adults, ranging from 5 L to 10 L. The water excess causes cerebral oedema,[1] with neurological features that include headache, nausea, weakness, lethargy, confusion, disorientation, blurred vision, muscle cramps, coma and seizures. These usually appear when the plasma sodium concentration is less than 125 mmol/L, but may also occur at higher sodium concentrations when there is a sudden fall in sodium, exceeding 15 mmol/L/24 hours.[2-5] Acute hyponatraemia with cerebral oedema is a medical emergency[6] requiring intravenous hypertonic saline.[7]

In contrast, chronic hyponatraemia may be well tolerated[3,8] — even with plasma sodium levels below 125 mmol/L — as the brain adapts to a lower extracellular fluid osmolality and prevents cerebral swelling by reducing intracellular fluid osmolar content.[2,4,9-11] Studies in a rat model of hyponatraemia suggest that osmolar equilibration is complete within 48 hours.[12] Thus, most clinicians distinguish acute from chronic hyponatraemia, when the latter exists for more than 48 hours.

Experimentally, the process of osmotic "adaptation" is faster than the process of osmotic "de-adaptation", with studies in chronically hyponatraemic dogs[13] and rats[12,14] revealing that rapid restoration of osmolality using hypertonic saline can cause dehydration of brain tissue[15] (an effect which is greater in the hyponatraemic animal than the normonatraemic one),[16] leading to central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM).[12,13,17]

CPM and EPM (eg, myelinolysis within the thalamus, basal ganglia, lateral geniculate nucleus or cerebellum) are non-inflammatory demyelination disorders (in contrast to the inflammatory demyelination disorder, multiple sclerosis). They are thought to be caused by neuronal cell apoptosis, which can be triggered by acute osmotic stress in a patient with prolonged nutritional disturbance.[18,19] CPM may be asymptomatic,[20] but is usually associated with clinical features that include dysarthria, dysphagia, pseudobulbar palsy, flaccid upper limb weakness ("man-in-the-barrel" syndrome)[21] or flaccid quadriparesis with a "locked-in" syndrome. EPM may also be asymptomatic, but is usually associated with clinical features that include tremor, ataxia, dystonia, mutism, Parkinsonism and catatonia. In a post-mortem study of 58 patients with non-inflammatory demyelination, 47% had CPM only, 31% had both CPM and EPM, and 22% had EPM only.[22]

Hyponatraemia is one of the most common disorders in clinical medicine and found in up to 80% of critically ill patients, yet despite rapid correction, CPM and EPM are rare and usually restricted to a few clinical situations that include chronic alcoholism (which is still the most common underlying condition in patients with CPM),[23] malnutrition, cachexia, prolonged diuretic use (with severe heart failure), anorexia nervosa (particularly with psychogenic polydipsia) and post-hepatic transplantation.[24] CPM and EPM are also more common when hyponatraemia is corrected in the presence of hypokalaemia,[25] hypophosphataemia,[26] hypomagnesaemia, sepsis or burns.[24]

CPM has also been reported in normonatraemic patients,[27,28] in normonatraemic patients with hypokalaemia[29,30] or hypophosphataemia,[31] and during correction of hypernatraemia[32] and hypophosphataemia.[29] A review of 170 patients with CPM suggested there is little clinical evidence for osmolar stress as the cause of CPM, as hyponatraemia was present in only 28% of patients and in most of these was corrected slowly; furthermore, the slow correction may have increased mortality.[33] This conclusion has been supported by others.[34,35] Nevertheless, experimental evidence linking the rapidity of correction of chronic hyponatraemia with CPM is persuasive.[12-14]

In patients who develop acute hyponatraemia, the urinary sodium concentration is often greater than 40 mmol/L, and the plasma urea concentration is low, whereas in chronic hyponatraemia, the urinary sodium concentration is usually less than 20 mmol/L, and the plasma urea concentration is often high.[36] Fluid restriction and reversal of any precipitating factor are often sufficient to manage chronic hyponatraemia[37] (and some suggest are the only way to prevent CPM and EPM[38]). However, if the patient is sodium-depleted (eg, has postural hypotension or prerenal failure), then 0.9% saline to correct the extracellular fluid and plasma volume deficit will be required to suppress antidiuretic hormone (ADH) release, improve renal perfusion and allow the excretion of free water to re-establish plasma sodium levels.

While the rate of correction of chronic hyponatraemia is generally recommended to be slow to reduce the incidence of CPM and EPM, at least nine correction rates have been reported: from 2–3 mmol/L/day up to 25 mmol/L/day.[18,24,33]

Nonetheless, the standard recommendation for many years has been to use a rate no greater than 12 mmol/L/day,[39-41] to be continued until the plasma sodium concentration is 130 mmol/L.[2,37,39,42,43]

However, the rate of rise in sodium concentration is often difficult to predict or control. A common experience is that the rise during the first day is surprisingly large — even when hypertonic saline is avoided, and a slow rise is attempted — as the sodium concentration seems to "run away".[24,44,45] The same happens in animal models.[24] The problem occurs in the patient with chronic hyponatraemia and hypovolaemia, as the rate of rise in plasma sodium concentration caused by the administration of 0.9% saline is complicated by a spontaneous diuresis and free water loss from the reduction in hypovolaemia-induced ADH secretion.

Fundamentally, plasma sodium is affected by changes to total body water as well as the total exchangeable sodium and potassium (a relationship described almost 50 years ago by Edelman et al[46]):

For example, $Na^+ = X/TBW$

Where Na^+ = plasma sodium (mmol/L)

$X = Na^+_{ex} + K^+_{ex}$ (mmol)

TBW = total body water (L)

Na^+_{ex} = total exchangeable sodium (mmol)

K^+_{ex} = total exchangeable potassium (mmol)

In a standard 70 kg man with 60% body weight as water (ie, 42 L) and a plasma sodium concentration of 140 mmol/L, the administration (or loss) of 42 mmol of sodium or potassium will increase (or decrease) the plasma sodium by 1 mmol/L, and the administration (or loss) of 1 L of water will decrease (or increase) the plasma sodium by more than 3 mmol/L.

Therefore, in the patient with hypovolaemia and chronic hyponatraemia treated with 0.9% saline, volume for volume the increase in plasma sodium generated by a spontaneous diuresis (assuming that the urinary sodium and potassium loss will be low),[36] will be at least twice that caused by the saline. However, to accurately predict this effect, the urine volume and sodium and potassium concentrations should be measured.

Although hypotonic solutions and 1-desamino-8-D-arginine vasopressin (DDAVP) have been recommended to counter the increase in plasma sodium concentration caused by the diuresis,[47] they must be used with care, as they may exacerbate hyponatraemia, particularly in patients who continue to drink (eg, with psychogenic polydipsia). Furthermore, as a review suggested that hypokalaemia is also a risk factor for CPM, and recommended it be corrected before correction of hyponatraemia,[25] it should be remembered that potassium replacement increases plasma sodium level — in an adult by about 1 mmol/L for every 40 mmol administered.

How, then, should one correct the plasma sodium level in a patient with chronic hyponatraemia?

- Most patients who receive sodium solutions do not suffer CPM. However, as CPM can develop despite slow correction[18,27,34,48] (with no rate of rise in plasma sodium concentration free of risk), patients at risk of CPM, such as the malnourished chronic alcoholic, should be identified before hyponatraemia is treated. Nutritional abnormalities (eg, vitamin deficiencies) and electrolyte abnormalities (eg, hypokalaemia, hypomagnesaemia and hypophosphataemia) should be managed along with the controlled correction of plasma sodium.
- Asymptomatic or mildly symptomatic patients can be treated by fluid restriction (even water deprivation) and reversal or cessation of precipitating factors (eg, thiazide diuretics).
- Patients with hypovolaemia should receive intravenous isotonic saline (initially 1 L may suffice), and currently it is recommended that the increase in plasma sodium should be no greater than 8 mmol/L on any day of treatment.[24,49]
- If an excessive diuresis develops, causing a rapid elevation in plasma sodium concentration, then DDAVP should be used, or, if intravenous hypotonic saline or dextrose and potassium solutions are to be used, then plasma concentrations and urinary excretion of sodium and potassium should be measured 2–4-hourly to accurately predict the change in plasma sodium concentration.

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References

1 Wasterlain CG, Posner JB. Cerebral oedema in water intoxication: I Clinical and chemical observations. *Arch Neurol* 1968; 19: 71-8.

2 Arieff AI. Hyponatraemia, convulsions, respiratory arrest and permanent brain damage after elective surgery in healthy women. *N Engl J Med* 1986; 314: 1529-35.

3 Arieff AI. Central nervous system manifestations of disordered sodium metabolism. *Clin Endocrinol Metab* 1984; 13: 269-94.

4 Arieff AI, Liach F, Massry SG. Neurological manifestations and morbidity of hyponatraemia: correlation with brain water and electrolytes. *Medicine* 1976; 55: 121-9.

5 Plum F, Posner JB. The diagnosis of stupor and coma. 3rd ed. Philadelphia: FA Davis, 1980.

6 Worthley LIG. Hyponatraemia and speed of correction: why is there a dilemma? *Crit Care Resusc* 2000; 2: 174-7.

7 Worthley LIG, Thomas PD. Treatment of hyponatraemic seizures with intravenous 29.2% saline. *BMJ* 1986; 292: 168-70.

8 Sterns RH. Severe symptomatic hyponatraemia: treatment and outcome. *Ann Intern Med* 1987; 107: 656-64.

9 Arieff AI, Guisado R. Effects of the central nervous system of hypernatremic and hyponatremic states. *Kidney Int* 1976; 10: 104-16.

10 Verbalis JG, Gullans SR. Hyponatraemia causes large sustained reductions in brain content of multiple organic solutes in rats. *Brain Res* 1991; 567: 274-82.

11 Gullans SR, Verbalis JG. Control of brain volume during hyperosmolar and hypoosmolar conditions. *Ann Rev Med* 1993; 44: 289-301.

12 Kleinschmidt-DeMasters BK, Norenberg MD. Cerebellar degeneration in the rat following rapid correction of hyponatremia. *Ann Neurol* 1981; 10: 561-5.

13 Kleinschmidt-DeMasters BK, Norenberg MD. Rapid correction of hyponatremia causes demyelination: relation to central pontine myelinolysis. *Science* 1981; 211: 1068-70.

14 Soupart A, Penninckx R, Crenier L, et al. Prevention of brain demyelination in rats after excessive correction of chronic hyponatremia by serum sodium lowering. *Kidney Int* 1994; 45: 193-200.

15 Sterns RH, Thomas DJ, Herndon RM. Brain dehydration and neurologic deterioration after rapid correction of hyponatremia. *Kidney Int* 1989; 35: 69-75.

16 Verbalis JG, Baldwin EF, Robinson AG. Osmotic regulation of plasma vasopressin and oxytocin after sustained hyponatremia. *Am J Physiol* 1986; 250: R444-51.

17 Laureno R. Central pontine myelinolysis following rapid correction of hyponatremia. *Ann Neurol* 1983; 13: 232-42.

18 Ashrafian H, Davey P. A review of the causes of central pontine myelinolysis: yet another apoptotic illness? *Eur J Neurol* 2001; 8: 103-9.

19 DeLuca GC, Nagy Z, Esiri MM, Davey P. Evidence for a role for apoptosis in central pontine myelinolysis. *Acta Neuropathol* 2002; 103: 590-8.

20 Newell KL, Kleinschmidt-DeMasters BK. Central pontine myelinolysis at autopsy: a twelve year retrospective analysis. *J Neurol Sci* 1996; 142: 134-9.

21 Deleu D, Salim K, Mesraoua B, et al. "Man-in-the-barrel" syndrome as delayed manifestation of extrapontine and central pontine myelinolysis: beneficial effect of intravenous immunoglobulin. *J Neurol Sci* 2005; 237: 103-6.

22 Gocht A, Colmant HJ. Central pontine and extrapontine myelinolysis: a report of 58 cases. *Clin Neuropathol* 1987; 6: 262-70.

23 Lampl C, Yazdi K. Central pontine myelinolysis. *Eur Neurol* 2002; 47: 3-10.

24 Martin RJ. Central pontine and extrapontine myelinolysis: the osmotic demyelination syndromes. *J Neurol Neurosurg Psychiatry* 2004; 75 Suppl 3: iii22-8.

25 Lohr JW. Osmotic demyelination syndrome following correction of hyponatraemia: association with hypokalemia. *Am J Med* 1994; 96: 408-13.

26 De Broucker T, Rueff B, Hammel P, Hadenque A. [L'hypophosphorémie: cause possible de myélinolyse centropontine.] *Presse Med* 1989; 18: 1166.

27 Bernsen HJ, Prick MJ. Improvement of central pontine myelinolysis as demonstrated by repeated magnetic resonance imaging in a patient without evidence of hyponatremia. *Acta Neurol Belg* 1999; 99: 189-93.

28 Mast H, Gordon PH, Mohr JP, Tatemichi TK. Central pontine myelinolysis: clinical syndrome with normal serum sodium. *Eur J Med Res* 1995; 1: 168-70.

29 Sugimoto T, Murata T, Omori M, Wada Y. Central pontine myelinolysis associated with hypokalaemia in anorexia nervosa. *J Neurol Neurosurg Psychiatry* 2003; 74: 353-5.

30 Bähr M, Sommer N, Petersen D, et al. Central pontine myelinolysis associated with low potassium levels in alcoholism. *J Neurol* 1990; 237: 275-6.

31 Michell AW, Burn DJ, Reading PJ. Central pontine myelinolysis temporally related to hypophosphataemia. *J Neurol Neurosurg Psychiatry* 2003; 74: 820.

32 Go M, Amino A, Shindo K, et al. A case of central pontine myelinolysis and extrapontine myelinolysis during rapid correction of hypernatremia. *Rinsho Shinkeigaku* 1994; 34: 1130-5.

33 Ayus JC, Krothapalli RK, Arieff AI. Changing concepts in treatment of severe symptomatic hyponatremia. Rapid correction and possible relation to central pontine myelinolysis. *Am J Med* 1985; 78: 897-902.

34 Omari A, Kormas N, Field M. Delayed onset of central pontine myelinolysis despite appropriate correction of hyponatraemia. *Intern Med J* 2002; 32: 273-4.

35 Tormey WP. Central pontine myelinolysis and changes in serum sodium. *Lancet* 1990; 335: 1169.

36 Humes HD. Disorders of water metabolism. In: Kokko JP, Tannen RL, editors. Fluids and electrolytes. Philadelphia: WB Saunders, 1986: 118-49.

37 Cluitmans FHM, Meinders AE. Management of severe hyponatremia: rapid or slow correction. *Am J Med* 1990; 88: 161-6.

38 Harris CP, Townsend JJ, Baringer JR. Symptomatic hyponatraemia: can myelinolysis be prevented by treatment? *J Neurol Neurosurg Psychiatry* 1993; 56: 626-32.

39 Sterns RH, Riggs JE, Schochet SS Jr. Osmotic demylination syndrome following correction of hyponatraemia. *N Engl J Med* 1986; 314: 1535-42.

40 Soupart A, Decaux G. Therapeutic recommendations for management of severe hyponatraemia: current concepts on pathogenesis and prevention of neurologic complications. *Clin Nephrol* 1996; 46: 149-69.

41 Pirzada NA, Ali II. Central pontine myelinolysis. *Mayo Clin Proc* 2001; 76: 559-62.

42 Laureno R, Karp BI. Pontine and extrapontine myelinolysis following rapid correction of hyponatraemia. *Lancet* 1988; 1: 1439-41.

43 Norenberg MD, Papendick RE. Chronicity of hyponatraemia as a factor in experimental myelinolysis. *Ann Neurol* 1984; 15: 544-7.

44 Berl T. Treating hyponatremia: damned if we do and damned if we don't. *Kidney Int* 1990; 37: 1006-18.

45 Berl T. Treating hyponatremia: what is all the controversy about? *Ann Intern Med* 1990; 113: 417-9.

46 Edelman IS, Leibman J, O'Meara MP, Birkenfeld LW. Interrelations between serum sodium concentration, serum osmolarity and total exchangeable sodium, total exchangeable potassium and total body water. *J Clin Invest* 1958; 37: 1236-56.

47 Soupart A, Ngassa M, Decaux G. Therapeutic relowering of the serum sodium in a patient after excessive correction of hyponatremia. *Clin Nephrol* 1999; 51: 383-6.

48 Leens C, Mukendi R, Foret F, et al. Central and extrapontine myelinolysis in a patient in spite of careful correction of hyponatremia. *Clin Nephrol* 2001; 55: 248-53.

49 Adrogué HJ, Madias NE. Hyponatremia. *N Engl J Med* 2000; 342: 1581-9. ❑