# Measuring intracerebral osmolytes in hyponatremic disorders.

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Hyponatremia is the most common electrolyte disorder diagnosed in the hospital setting (1). Patients develop nausea and malaise when the plasma sodium concentration decreases from a normal level of 140 to ~ 125 mM (2). When the plasma sodium concentration falls below 120 mM, lethargy, headache, and seizures may occur (2). These gastrointestinal and neurologic symptoms have been attributed to cerebral edema which is present during the first few days after the decrease in plasma sodium (2–4). Importantly, permanent neurologic sequelae rarely develop, except possibly in premenopausal women (5–6). What are the known volume regulatory mechanisms which minimize cerebral edema thereby preventing prolonged swelling of the brain? Studies in animals have focused on three important adaptive responses which result in the normalization of cerebral volume. First, within minutes after the development of brain edema, the increase in cerebral interstitial hydrostatic pressure causes interstitial fluid to flow into the cerebrospinal fluid (7, 8). Excess fluid in the cerebrospinal space then enters the systemic circulation via the arachnoid villi. Second, and quantitatively most important, is the osmotic loss of water due to cellular efflux of sodium and potassium salts. This response is maximal in less than 24 h (9–11). The final regulatory process is the loss of organic osmolytes which accounts for ~ $^1/_3$ of the total decrease in cerebral osmole content (12–14). The particular organic compounds involved were unknown until recently, and were fittingly called "idiogenic osmoles."

The brain's utilization of organic osmolytes for volume regulation is not unique. Organic osmolytes are used by numerous prokaryotic and eukaryotic cells to osmoregulate (15–24). These compounds can be conveniently subdivided into three groups: (*a*) polyols, (*b*) neutral amino acids, and (*c*) methylamines and urea (25). The particular organic osmolyte utilized is both organism and organ specific. Previous studies in mice and rats have demonstrated that during chronic hyponatremia, the brain content of glutamate, glutamine, taurine, glycerophosphorylcholine, phosphocreatine/creatine, and myoinositol are significantly decreased (12–14).

What is the clinical significance of these changes in brain organic osmolyte content? Several predictions can be made if one assumes that (*a*) the decrease in cerebral osmole content is a slow process requiring days for completion, (*b*) cerebral volume normalizes only when the loss of organic osmoles is maximal, and (*c*) clinical symptoms correlate with the degree of cerebral edema. The first prediction is that hyponatremia which develops slowly over several days is less likely to be associated with gastrointestinal or neurologic symptoms. This is what has been observed clinically (2). Second, severe acute hyponatremia should result in maximal cerebral swelling and morbidity. Interestingly, premenopausal women appear to be uniquely susceptible to severe acute hyponatremia and develop permanent neurologic sequelae associated with cerebral edema and herniation (6, 26). It has been hypothesized that these women have less efficient mechanisms for minimizing cerebral edema following the initial influx of water induced by hyponatremia (6, 26). In contrast, data obtained from a survey of practicing nephrologists suggests that severe acute hyponatremia (sodium concentration ≤ 105), does not result in neurologic damage (5). Furthermore, age, sex, and hypoxic episodes were unrelated to clinical outcome. It is clear that a randomized prospective trial is required to determine whether sex differences play a role in the adaptation to acute hyponatremia.

The normalization of cerebral volume in the presence of chronic hyponatremia (> 48 h of duration), creates a dilemma for the clinician. Experimental data from animals suggests that the rapid correction of the plasma sodium concentration results in brain shrinkage because of the slow recovery of several organic osmolytes (9, 10, 13, 27). Moreover, an overshoot in cerebral sodium and chloride content has been described (13). It is generally accepted that the rapid correction of chronic severe hyponatremia (> 12 meq/liter in the first 24 h, or > 18 meq/liter in the initial 48 h of therapy) can cause the osmotic demyelination syndrome (5, 28). This syndrome first described by Adams et al. (29) is characterized by demyelinating lesions in the pons (central pontine myelinolysis), basal ganglia, thalamus, corticomedullary junctions, and periventricular white matter. Patients develop delayed (2–6 d) pseudobulbar palsy, spastic quadraparesis, stupor, coma, and death. Several possible mechanisms have been postulated for the loss of myelin with preservation of neuronal axons and cell bodies: (*a*) physical shearing of axons from their myelin sheaths with subsequent loss of myelin, (*b*) an overshoot in cell sodium and chloride content with low organic osmolyte levels, and (*c*) cell anoxia resulting from brain shrinkage. Clearly, further experiments are required to address these possibilites.

Magnetic resonance imaging (MRI) is the imaging technique of choice to detect demyelinating brain lesions (30, 31). However, MRI is not sufficiently sensitive to resolve mild demyelination and may not demonstrate lesions until a month after the onset of symptoms. In this issue of *The Journal,* (32) Videen et al. have used proton magnetic resonance spectroscopy (MRS) to measure changes in intracerebral organic osmolytes in 12 patients with moderate chronic hyponatremia (sodium ~120 meq/liter) (33, 34). The authors measured the cerebral osmolyte content in occipital grey and parietal white matter. Myoinositol was decreased to the greatest extent. Significant reductions in choline containing compounds, creatine/phosphocreatine and *N*-acetylaspartate were also detected. Grey matter osmolytes were remeasured in four treated patients at follow-up 8–14 wk later (mean plasma sodium 131 meq/liter). Difference spectra clearly demonstrated a significant recovery of myoinositol, choline containing compounds, and *N*-acetylaspartate. In the one patient who had a normal plasma sodium (139 meq/liter) at 14 wk, all four osmolytes recovered completely. No patients developed osmotic demyelination syndrome.

The study by Videen et al. demonstrates that proton MRS is an important new tool for assessing the changes in cerebral osmolytes in patients with hyponatremia. Further experiments are needed to measure the time course of these changes during the generation and recovery phases of hyponatremia, respec-

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tively. An important question is whether measurements of cerebral osmolytes can be used to predict the development of the osmotic demyelination syndrome. The answer to this question may determine whether cerebral proton MRS studies will be helpful in the therapy of a given patient with severe chronic hyponatremia, for calculating the appropriate rate of correction of the plasma sodium concentration.

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