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Does Uremia Protect against the Demyelination Associated with Correction of Hyponatremia during Hemodialysis? A Case Report and Literature Review

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ABSTRACT

Rapid correction of chronic hyponatremia is known to cause demyelination syndromes, which are attributed to the rapid shift of water out of the brain. In uremic patients with hyponatremia, depending on the dialysate sodium concentration and delivered Kt/V, serum sodium levels may be rapidly corrected inadvertently during the hemodialysis (HD) session. It is not known whether uremic patients are as susceptible to the development of demyelination as patients with normal renal function. Since urea diffuses slowly across the blood–brain barrier, it can act as an effective osmole between plasma and the brain if levels are changed abruptly. During HD, blood urea levels drop suddenly and significantly and cerebral edema may develop (dialysis disequilibrium syndrome). This effect may counteract the fluid shift out of the brain during correction of hyponatremia. Therefore, theoretically, uremic patients may be less prone to develop demyelination. We present a patient with renal failure whose hyponatremia was corrected rapidly during HD to illustrate the potential problem. The patient tolerated rapid correction of hyponatremia without sustaining any neurologic damage. We performed a literature search looking for similar case reports and reviewed the scientific evidence behind the above hypothesis.

Rapid correction of chronic hyponatremia is well known to cause myelinolysis, a neurologic disorder manifested by spastic quadriparesis, pseudobulbar palsy, and mental disorders ranging from confusion to coma (1). The pathogenesis is attributed to the development of brain dehydration. The brain is freely permeable to water, but osmotic adaptation of brain solutes takes time. When hyponatremia is rapidly corrected, blood becomes relatively hypertonic to the brain with a resultant shift of water out of the brain (2).

Conversely "dialysis disequilibrium syndrome" develops when a uremic patient's blood urea nitrogen (BUN) is lowered too rapidly during hemodialysis (HD). The development of cerebral edema is the likely cause of this syndrome. However, the exact mechanism responsible for the development of edema is still debated (3). Therefore it is plausible that patients with a high BUN from renal failure and hyponatremia may not be as vulnerable as patients with normal renal function to the development of cerebral dehydration and myelinolysis when hyponatremia is rapidly corrected during HD.

We describe a patient with acute on chronic renal failure and hyponatremia who was treated with HD for hyperkalemia. The patient tolerated the procedure well without any adverse neurologic effects despite a serum sodium correction rate of 3 mEq/L/hr. The case is used to investigate the potential problem associated with rapid correction of hyponatremia during HD. We also performed a literature review on this topic with particular attention to case reports of myelinolysis in uremic patients whose hyponatremia was rapidly corrected during HD.

Case Report

A 61-year-old man was evaluated at an outside hospital emergency room for a generalized feeling of unwellness and weakness for 10 days. Potassium was 6.9 mEq/L, BUN was 77 mg/dl, and serum creatinine was

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7 mg/dl. Intravenous fluids were administered to treat suspected volume depletion. Oral Kayexalate was given to lower the serum potassium concentration. However, the patient remained oliguric and was transferred to our institution.

Pertinent past medical history included a cadaver renal transplant 10 months earlier with a baseline serum creatinine of 2–2.5 mg/dl. No major transplant-related complications were present. His end-stage renal disease (ESRD) was from chronic glomerulonephritis. Medications included cyclosporine, azathioprine, prednisone, diuretics, coumadin, diltiazem, and lisinopril.

On arrival, the patient was febrile with tachycardia and tachypnea. Blood pressure was 125/75 mmHg. Bilateral basilar rales were noted. Laboratory data showed serum sodium, 119 mEq/L; potassium, 6.6 mEq/L; chloride, 90 mEq/L; bicarbonate, 17 mEq/L; glucose, 100 mg/dl; and an unchanged BUN and serum creatinine. Urinalysis revealed large blood, +3 protein, leukocyte esterase, and many red and white blood cells. Electrocardiogram (EKG) demonstrated atrial fibrillation at a rate of 120/min and prominent peaked T waves in the chest leads. Chest radiograph showed early pulmonary congestion.

The patient was felt to have developed acute renal failure from urosepsis. Blood and urine cultures were obtained and broad-spectrum antibiotics started. Due to the patient's oliguric state and hyperkalemia with EKG changes, the patient underwent HD for 3 hours with a dialysate bath of sodium 135 mEq/L and potassium 2 mEq/L. Following dialysis, laboratory results showed the following: sodium, 128 mEq/L; potassium, 4.1 mEq/L; BUN, 54 mg/dl; and serum creatinine, 5.6 mg/dl. The change in serum sodium level was 9 mEq in 3 hours. The patient's neurologic status remained unchanged. During the subsequent 2–3 days, the patient's sodium remained at 126–129 mEq/L. Blood and urine cultures grew *Klebsiella oxytoca*. The patient's urine output and general condition slowly improved, requiring no further dialysis. Neurologic status was normal.

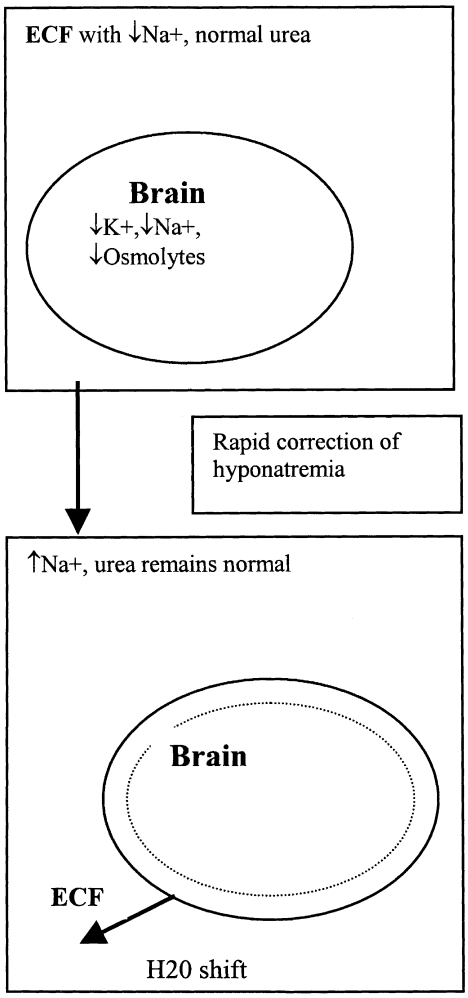

FIG. 1. Schematic diagram of brain volume changes in response to correction of chronic hyponatremia in nonuremic subjects. Solid line represents brain volume before correction; dashed line represents after rapid correction (brain cell shrinkage).

Discussion

When faced with osmolar changes in the plasma, the brain has adaptive mechanisms to regulate its volume within a rigid skull. During hyponatremia, cerebral edema is limited by adaptive loss of brain solutes that consist of both electrolytes and osmolytes (4–6). During the development of hyponatremia, sodium and chloride are lost into the cerebrospinal fluid (CSF) within minutes and the concentration of potassium in the brain decreases within 2–3 hours. Within the next 48 hours the brain also loses intracellular organic osmolytes such as glutamine, taurine, *myo*-inositol, and phosphocreatinine. Most adaptive measures are achieved in 48 hours. Water content in the brain returns to normal and remains stable thereafter (Fig. 1).

Following correction of hyponatremia, reaccumulation of electrolytes and organic osmolytes take place in the brain. Electrolytes, particularly sodium and chloride, reaccumulate rapidly within 24 hours, with an overshoot before returning to normal levels. Organic osmolytes return to normal levels at a much slower rate, taking 5–7 days (7). If chronic hyponatremia is corrected rapidly before these adaptive mechanisms are complete, blood becomes hypertonic relative to the brain, with a resultant shift of water out of the brain. This effect can lead to cerebral dehydration and myelinolysis (2,7). Formerly called central pontine myelinolysis, myelinolysis is now known to occur also in extrapontine brain areas such as the midbrain and medulla. Animal experiments and retrospective analyses in humans suggest that the risk of myelinolysis is greater with more rapid correction of hyponatremia and correction of hyponatremia that develops in chronic (more than 48 hours) rather than acute settings. The symptoms tend to occur 2–3 days following correction of the serum sodium (1). It has been suggested that the rate of correction of asymptomatic chronic hyponatremia should not exceed 0.5 mEq/L/hr, 10 mEq/L in the first 24 hours, and not more than 18 mEq/L in the first 48 hours. In symptomatic hyponatremia, the correction rate may go up to 1.5–2 mEq/L/hr for

the first 3–4 hours, but still not exceeding 12 mEq/L in the first 24 hours (1,8–10).

The usual methods of correction of hyponatremia include water restriction and administration of hypertonic saline. Administration of urea (both oral and intravenous routes) has also been used to safely correct hyponatremia in humans. Urea corrects hyponatremia by inducing an osmotic diuresis with free water loss and by reducing renal sodium excretion secondary to passive sodium reabsorption in the thin ascending limb (8,11). It has been reported in a rodent model that when hyponatremia is corrected with urea as compared to hypertonic saline, the risk of developing myelinolysis is decreased from 89% to 39% (12). The mechanism by which urea prevents the development of brain lesions remains hypothetical. Although urea diffuses easily across most cell membranes, it diffuses more slowly into the brain. When urea is infused, it only takes 1 hour for plasma urea to equilibrate with muscle water, whereas it takes 4–10 hours to equilibrate in the brain and CSF (13). It is also reported to trigger or stimulate the recovery of brain organic osmolytes (14).

"Dialysis disequilibrium syndrome" is believed to be due to cerebral edema that develops when plasma urea concentration drops rapidly during HD (reverse urea effect). It has been demonstrated in rat models that during acute azotemia until equilibrium is reached across the brain cell membranes, urea is an effective osmole (14). This study also showed that acute azotemia is a hypertonic state and urea triggers adaptive processes causing cerebral accumulation of organic osmolytes, preventing the shift of water to the extracellular fluid (ECF) and cerebral dehydration (14). In fact, Soupart et al. (15) recently demonstrated that rapid reaccumulation of brain organic osmolytes, in particular *myo*-inositol and taurine, occurs in azotemic rats after correction of chronic hyponatremia. Synthesis of transporters for these organic osmolytes (*myo*-inositol) may be stimulated by the uremic milieu (15).

These data suggest that if plasma urea concentrations are rapidly reduced or increased, osmolar gradients may result between plasma and the brain until equilibrium is achieved. Therefore these findings raise the question of whether elevated blood urea levels would protect uremic patients from the development of demyelinating syndromes when hyponatremia is rapidly corrected.

The exact etiologic agent or the mechanism responsible for dialysis disequilibrium syndrome is still being debated. Some evidence points to the reverse urea effect, while some points to the formation of organic acid idiogenic osmoles in the brain (16–18). Theoretically renal failure patients with a high blood urea level should tolerate a rapid correction of hyponatremia (Fig. 2). Clinically it might be reasonable to assume that no matter whether urea or idiogenic osmoles contribute to cerebral swelling after HD, these substances could also prevent cerebral dehydration when hyponatremia is rapidly corrected during HD.

We performed a literature search looking for case reports of the rapid correction of hyponatremia in the dialysis population. Three were noted; two did not develop the demyelination syndrome (19,20). One patient with severe hyponatremia developed osmotic demyelination syndrome following hemodialysis (21). In contrast, there is an abundance of literature on development of demyelination in general medical patients when hyponatremia is rapidly corrected (1).

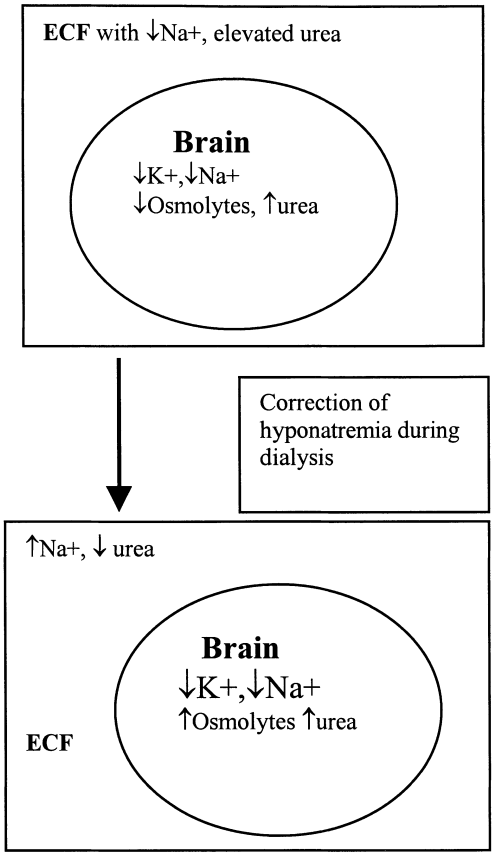

FIG. 2. Schematic diagram of brain volume changes due to correction of chronic hyponatremia in uremic subjects. The elevated urea in the brain and the formation of organic osmolytes prevents the development of an osmotic gradient from the correction of hyponatremia during hemodialysis.

In our patient, the duration of hyponatremia was probably longer than 48 hours given the patient's presenting history. As the patient did not have any neurologic signs and symptoms, routine brain imaging to detect demyelination was felt to be unnecessary and was not done after the correction of hyponatremia. Our patient's initial serum sodium (119 mEq/L) was higher than in many reported cases with demyelination, where the serum sodium tended to be less than 115 mEq/L. This may have contributed to the favorable outcome of our patient without any adverse neurologic outcome.

There is theoretical and experimental animal evidence that uremic subjects should tolerate a rapid correction of hyponatremia better than nonuremic subjects. It has been shown that in rats with renal failure, excessive correction of hyponatremia is associated with significantly lower risk of neurologic complications and death compared with rats in the control group that had no azotemia (4). This effect appears to be due to some combination of rapid reaccumulation of brain organic osmolytes and increased brain cell urea content (15). To

what extent hyponatremia can safely be corrected in humans during HD has not, to our knowledge, been studied. Until human data are available, caution should still be exercised in correcting chronic hyponatremia in uremic patients. Serum sodium should be corrected in patients with renal failure during HD using the guidelines currently accepted for correction of hyponatremia in nonuremic patients (22). Available tables should be consulted to predict the postdialysis serum sodium levels given the Kt/V and the dialysate sodium bath being used (23).

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