

RESEARCH LETTER

Successful Treatment of Adult Cerebral Salt Wasting With Fludrocortisone

Hypnatremia following cerebral trauma has commonly been attributed to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Cerebral salt wasting (CSW) can lead to a similar clinical picture, for which treatment is not well defined.

Report of a Case. A 75-year-old man presented with a 3-week history of worsening ataxia following blunt head trauma in a motor vehicle crash 1 month earlier. His history included uncomplicated type 2 diabetes mellitus and hypertension, managed with rosiglitazone, 4 mg/d, and ramipril, 2.5 mg/d. The patient was confused and had marked truncal ataxia. Central venous pressure was low at 3 mm Hg, indicating volume depletion. Euglycemia and normotension were maintained following the discontinuation of both rosiglitazone and ramipril therapies.

A computed tomographic scan of the brain demonstrated acute and chronic bilateral frontoparietal subdural hematomas measuring up to 22 mm in the maximum dimension, with shift of the septum pellucidum to the right by 5 mm and subfalcine herniation. Findings from serum biochemical analysis demonstrated a serum sodium level of 123 mEq/L (137-146 mEq/L) (milliequivalents per liter to millimoles per liter is a 1-to-1 conversion); an osmolality of 259 mOsm/kg (275-295 mOsm/kg) (milliosmoles per kilogram to millimoles per kilogram is a 1-to-1 conversion), a uric acid level of 0.34 mg/dL (4.2-8.4 mg/dL) (to convert to micromoles per liter, multiply by 59.485), a urinary sodium level of 236 mEq/L; and a urinary osmolality of 825 mOsm/kg. Hypothyroidism, hypoadrenalism, and liver and renal failure were excluded from serum biochemical analysis. Findings from serum biochemical analysis performed 1 month prior immediately following the motor vehicle crash were normal.

Bilateral burr holes were made for drainage, with subsequent reduction in size of bilateral hematomas. Hyponatremia was corrected with 3% hypertonic saline. Withdrawal of hypertonic saline 3 days later led to a decrease in serum sodium level to 120 mEq/L (**Figure**). Hypertonic saline was reintroduced to maintain a serum sodium level above 125 mEq/L. A repeated attempt to withdraw hypertonic saline 3 days later again led to a fall in serum sodium level with persistent inappropriate natriuresis (Figure). N-terminal pro-brain natriuretic peptide level was not elevated. Plasma renin activity and aldosterone concentration measured on day 6 were undetectable. Treatment with fludrocortisone was com-

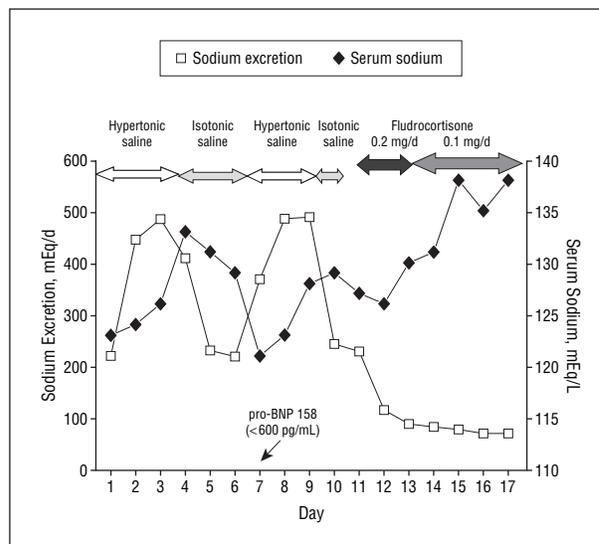


Figure. Changes in serum and urinary sodium concentration with treatment. For serum sodium, milliequivalents per liter to millimoles per liter and, for pro-brain natriuretic peptide (pro-BNP), picograms per milliliter to nanograms per liter are 1-to-1 conversions.

menced initially at 0.2 mg/d and later reduced to 0.1 mg/d, and a rapid reduction in natriuresis and restoration of serum sodium level to the normal range was observed (Figure).

Comment. Both CSW and SIADH are associated with hyponatremia, hypouricemia, and inappropriately high urinary sodium concentration and osmolality. The only distinguishing features are signs of volume depletion. It has been postulated that CSW is a centrally mediated process, possibly via secretion of natriuretic peptides¹ or disrupted sympathetic neural input to the proximal tubules.² Serum N-terminal pro-brain natriuretic peptide level was not elevated in our case.

Scattered case reports in the pediatric population demonstrated suppressed plasma renin activity and plasma aldosterone concentration in CSW, while plasma aldosterone concentration usually remained normal or high in SIADH,^{3,4} although this is not a universal finding. While hyporeninemic hypoaldosteronism can be a manifestation of renal tubulopathy in type 2 diabetes, prior normal findings from serum biochemical analysis excluded it as a preexisting contributing complication in our patient.

Fludrocortisone has been used to prevent ischemia in patients with subarachnoid hemorrhage,⁵ but its use in other cerebral pathologic conditions is poorly studied.^{3,4,6} Hyponatremia not responding to fluid restriction should raise the concern of undiagnosed CSW, which may be supported by excessive natriuresis and suppressed plasma renin activity and plasma aldosterone concentration. The lack of sustained response to hyper-

tonic saline led to our empirical trial of fludrocortisone, which was later supported by the results of suppressed plasma renin activity and plasma aldosterone concentration. Early administration of fludrocortisone may alleviate the need of hypertonic saline infusion and shorten hospital stay.

In conclusion, we describe the biochemical changes in a case of CSW and its successful response to fludrocortisone therapy. Although the mechanism of inappropriate hyporeninemic hypoaldosteronism in CSW remains uncertain, and it may not be universal in all cases of CSW, the current case indicates that fludrocortisone therapy may be of benefit in selected adult patients with CSW and refractory hyponatremia.

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Financial Disclosure: None reported.

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COMMENTS & OPINIONS

Prevalence of Type 1 Gaucher Disease in the United States

The study by Landgren et al¹ investigated the risk of malignancy in patients with type 1 Gaucher disease (GD). We have several questions about their article that address the validity of the findings. First, we are concerned by the large number of patients with reported type 1 GD. The prevalence of type 1 GD is 1:40 000 to 60 000 in the general population and 1:500 to 800 among Ashkenazi Jews.²⁻⁶ Recognizing that Ashkenazi Jews constitute no more than 2% to 3% of the US population, fewer than 200 patients with GD should be expected among 4.5 million Department of Veterans Affairs (VA) hospital patients. The authors found 1525. The authors attribute the high prevalence of GD to the study

being hospital based. However, a national hospital-based study in Spain, using demographic, clinical, diagnostic, and radiological data for patient identification, found only 75 patients with GD⁷—numbers even lower than those predicted from other European studies.

Second, the authors did not report how many of their patients (mean age at study entry, 51.1 years) had died. Because a 50-year-old patient with type 1 GD can expect to live an additional 27.2 years,⁸ most of the 1525 VA patients should be alive. However, only about 250 male US patients older than 50 years are enrolled in the International Gaucher Registry.⁹ It might be argued that the Registry enrollment favors patients with more severe phenotypes, whereas the VA patients identified by the authors have clinically mild disease. However, it seems to us unlikely that patients would be hospitalized without significant symptoms. Moreover, the probability that patients with mild GD will come to diagnosis in any medical setting is low. Only 1 of 5 North American hematologists suspected GD when presented with a hypothetical patient with 6 of its common signs and symptoms.¹⁰ Furthermore, more than 250 glucocerebrosidase gene mutations and polymorphisms have been identified, and those associated with mild as well as more severe phenotypes have been well characterized in terms of their population frequencies.⁹ It seems unlikely that a unique, sizeable population of mildly affected patients with type 1 GD has thus far eluded discovery.

Third, as the authors point out, the *International Classification of Diseases (ICD)* codes for GD are nonspecific and include other lipid disorders. Although the *ICD, Ninth Revision* code 272.7 is more restrictive, it includes other lysosomal storage diseases such as Fabry disease, which although rarer than GD, should not be discounted, especially among male patients. The *ICD, Eighth Revision* code 272.2 was substantially less specific and included multiple lipid disorders including hypercholesterolemia. The diagnosis of GD can be validated preferably either by enzyme assay or mutation analysis, or minimally, by comprehensive clinical review.

We believe that a confirmation of the GD cases by direct examination of records is required, and we raise the question as to whether such a validation was done. If not, we propose that this be completed to affirm the validity of the diagnosis of GD, especially in light of our concerns about the lack of specificity of the *ICD* coding.

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