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# The Evolving History of the Diagnosis and Treatment of SIADH and CSW

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## ABSTRACT

For decades the diagnosis and treatment of SIADH has evolved while the syndrome of cerebral salt wasting has been ignored or ever doubted. However, the recognition of CSW has increased and clouded the diagnosis and treatment of because it shares the same laboratory footprint as SIADH. We present the evolving history pertaining to the diagnosis and treatment of SIADH and CSW.

**Keywords:** SIADH; CSW; Hyponatremia

## INTRODUCTION

Cerebral salt wasting is frequently encountered in neurosurgical units. Neurologists and neurosurgeons consider this the cause of hyponatremia in many of their patients. This is counter to the oft repeated articles stating that CSW is very rare, or possibly non-existent, but rather a form of syndrome of inappropriate antidiuretic hormone, SIADH.

The conundrum of differentiating CSW from SIADH exists because both syndromes cause hyponatremia and share the same laboratory parameters such as plasma Na <135 mEq/L, plasma osmolality < 275 mOsm/L. , urine Na > 40 mEq/L, urine osmolality > 100 mOsm/L. with normal cardiac, hepatic, adrenal, renal and thyroid function.

Peters described cerebral salt wasting in 1950, being present in patients with cerebral disease.[1] Within a few years this assertion was dismissed, and the Peters cases were considered a form of SIADH because they shared the same laboratory parameters mentioned above. In 1957 Schwartz described hyponatremia in a patient due to inappropriate secretion of antidiuretic hormone from a tumor.[2] The criteria, above, for SIADH were reiterated and published in 1967.[3]

Nelson reignited the existence of CSW in 1981, publishing a manuscript that described 12 neurosurgical patients (mostly with subarachnoid hemorrhage) who met all of the criteria for SIADH but were found to be hypovolemic using isotope dilution techniques, thus bringing attention to the fact that SIADH and CSW were two distinct causes of hyponatremia, "water-retaining patients with SIADH" and "salt wasting patients with CSW". [4]

During the next several decades there were numerous reports of SIADH that caused hyponatremia which were not due to a tumor, but due to such diverse causes as infections, head trauma, autoimmune diseases and bone fractures.[5-8]

Why do so many unrelated conditions cause hyponatremia, and if not due to tumor induced inappropriate ADH secretion what is the pathophysiology.
Since 2000 many reports have revealed that inflammation can release cytokine IL-6 which directly induces the inappropriate secretion of ADH from the hypophysis causing another form of SIADH, not related to the presence of a tumor.[9-11]

Thus, many of the lists of causes of SIADH likely include the classic syndrome of inappropriate antidiuretic hormone (SIADH) by a tumor,[12] as well as hyponatremic cases related to inflammatory cytokine IL-6 induced inappropriate ADH secretion, which should probably be called Type 2 SIADH, while tumor induced SIADH should be called Type 1 SIADH. Additionally, CSW, with appropriate secretion of ADH may be responsible for hypovolemia-induced ADH secretion and hyponatremia. Unfortunately, all three entities present identical laboratory parameters but require radically different treatment.

After years of research concerning urate excretion Maesaka observed an interesting phenomenon regarding fractional excretion of urate [FEurate], the transport of urate being solely handled in the proximal renal tubule. Patients with true SIADH have elevated FEurate while hyponatremic but which normalizes after correction of hyponatremia but patients with CSW have elevated FEurate while hyponatremic and even after correction of serum sodium.[13,14] The mechanism responsible for correction of FEurate in SIADH is currently unknown.

In 2021 Maesaka et al. reported finding a proximal tubule natriuretic factor in neurosurgical patients.[15]
Using an algorithm based on determination of FEurate and response to isotonic saline infusions and ignoring reliance on assessing volume status or on urine sodium, plasma levels of renin, aldosterone or ANP/BNP 62 patients with hyponatremia, without renal insufficiency, cirrhosis, nephrosis or congestive heart failure were recruited. Based on the above statement regarding normalization or persistence of FEurate, 17 patients had SIADH, 19 had reset osmostat(RO), 24 had RSW, 1had hyponatremia due to Hydrochlorothiazide and 1 had hyponatremia due to Addison disease. Of the 24 patients with RSW, 21 had no clinical evidence of cerebral disease. They were given isotonic

saline infusions which induced dilute urine excretion in 19 patients while 10 required dextrose and water to retard the resulting rapid increase in sodium due to the resolution of hypovolemia and the quick inhibition of ADH secretion. Twelve of the patients had persistently increased FE urate after correction of hyponatremia which was possibly due to persistence of the inflammatory condition, and persistence of the natriuretic factor.[16]

They induced salt wasting in rats by infusing plasma of neurosurgical and Alzheimer patients, identifying haptoglobin related protein without signal peptide (HPRWSP) as the proximal tubule factor responsible for increasing sodium wasting as well as urate wasting.[17]

The difficulty differentiating SIADH from CSW is due to the perplexing fact that they share the same lab criteria as originally described in 1967. Also contributing to inability to reliably diagnose is the inability to assess the volume status which requires the availability of sophisticated point of care ultrasound of the heart, lung or inferior vena cava when treating a severely symptomatic patient with hyponatremia.[18,19] Physical examination at the bedside regarding hypervolemia, hypovolemia or euvolemia is undependable and unpredictable.[20]

The physician must always consider other causes of hyponatremia which might include psychogenic polydipsia, beer potomania, and a long list of medications [1] – arginine vasopressin (AVP) analogues such as desmopressin and oxytocin, agents that stimulate antidiuretic hormone (ADH) release (vincristine, ifosamide), agents that increase the expression or activity of the V2-receptor water channels in the collecting duct which increases water reabsorption -- cyclophosphamide, chlorpropamide e, carbamazepine, selective serotonin reuptake inhibitors (SSRIs- Sertraline, Fluoxetine and others), non-steroidal anti-inflammatory drugs, which inhibit the prostaglandins that normally antagonize ADH and indirectly result in water retention, cisplatin which decreases ADH sensitivity in the collecting duct, resulting in volume depletion and appropriate secretion of ADH, 3-4 methylenedioxymethamphetamine (MDMA, “Ecstasy”, or “Molly”) which indirectly, through serotonin, induces ADH secretion, coupled with the “dipsogenic” effect of stimulating intense thirst, thiazide diuretics , or even a hereditary upregulation of the V2-receptor.[21]

In addition, hyponatremia may also result from organ dysfunction in which clinical clues may lead to proper diagnosis and treatment. The abbreviated physiology which causes hyponatremia in these cases most often relates to increased antidiuretic hormone (ADH) in response to perceived reduction in effective blood volume (EBV) as in congestive heart failure[22], hypothyroidism[23], cirrhosis with portal hypertension and ascites[24] , salt wasting in aldosterone deficient patients with primary adrenal insufficiency (Addison’s disease) or in primary pituitary insufficiency[25] where deficiencies in adrenocorticotrophic hormone (ACTH) result in downstream insufficiencies of aldosterone, thyroid hormone and cortisol, as well as other hormones.

**Treatment protocols**

In the absence of historical and/or physical clues indicating the cause of hyponatremia, and in the presence of an emergency such as a seizing patient with hyponatremia, a physician is confronted with treatment, treatment that is radically different whether the patient has Type 1 SIADH, Type 2 SIADH or CSW. Unable to wait for sonograms, or blood and urine findings, the decision may be fluid-depleting the SIADH patient or fluid-repleting the CSW patient.

Choosing the wrong treatment can lead to catastrophic results such as osmotic demyelination syndrome (ODS) or death.

Suggested treatments for SIADH include water restricting or increasing water excretion with SGLT2 i– sodium-glucose transporter inhibitors[26], Declomycin[27], urea[28], urea transporter inhibitors[29], vasopressin receptor antagonists (vaptans)[30] or loop diuretics[31], versus giving fluids and volume to the hypovolemic patient with CRSW.[32,33] The current use of urea transporter inhibitors and SGLT2-inhibitors are currently being evaluated for safety. Calling a consultant nephrologist for advice is warranted but may delay treatment when urgent treatment is paramount.

United states guidelines for treating hyponatremia were published in 2013 but did not address CSW.[34]

Normal saline might correct serum sodium in patients with SIADH and only if associated with a degree of water volume restriction or treatment with a volume depleting agent – a dangerous error if the patient actually has CSW. Small volumes of hypertonic saline can quickly improve serum sodium to a safer range while avoiding the possible error of fluid restricting a patient with CSW. The small volume administered quickly inhibits the potent volume stimulus for ADH secretion in these patients.

A safe and unifying treatment guideline which can prevent delay in treatment of severe, life-threatening hyponatremia was published in 2014, allowing a physician to immediately treat before ascribing the syndrome to either SIADH TYPE 1, SIADH TYPE 2 or CSW.[35] In 2014 The European Society of Endocrinology (ESE), European Renal Association and the European Renal Best Practice Group published a treatment recommendation that would avoid the anxiety of making an error.

However this recommendation was dismissed in an editorial which cited that the EU CPG guidelines expressed a divergent interpretation of evidence regarding the quality of evidence of the vaptan clinical trials, largely because they were industry sponsored, expounding a USA perspective.[36] Importantly, Verbalis is correct in recommending tolvaptan for SIADH. However, it is not correct for the treatment of hyponatremia due to CSW, volume depleted patients likely to have a high Uosm, as alluded to by Avila.[37]

The ESE method recommends administration of a 150-cc. bolus of 3% saline over 20 minutes via a peripheral vein, repeating serum sodium after 20 minutes – then repeating another 150-cc. bolus of 3% saline, if necessary, to increase serum sodium by 4-6 mEq/L. within 4-6 hours and certainly not more than 8 - 10 mEq/L within 24 hours, They included the US recommendation to restrict correction to less than 8 mEq/L for patients at high risk for ODS – alcoholism, malnutrition, hypokalemia, severe liver disease, or serum sodium < 105 mEq/.[38,39]

Small increases in serum sodium will prevent further brain cell swelling while "braking" the increase in serum sodium by using continuous intravenous infusion of .45% saline or dextrose and water after the bolus reduces the chance of brain cell shrinkage and ODS.

Despite the 2014 ESE treatment recommendation a survey in 2025 found a real-time difference between physicians in the UK versus physicians in the remaining western European countries – 85% of UK physicians versus 33% of other European physicians using the bolus therapy.[40] The divergence may be due to continued uncertainty regarding rate of correction, the diagnosis, the unavailability of 3% saline, or hospital regulations regarding route of administration (central venous line versus peripheral vein), or location of the patient outside of an acute care site.

MacMillan et al. described rapid correction of serum sodium was common, with 18% of hyponatremic patients correcting sodium> 8 mEq/L but ODS rare at 0.14%. The authors inferred that factors other than the correction rate, not yet identified, may be implicated in the development of ODS.[41] Contrarily, another study reported that ODS was rare and manly associated with rapid correction.[42]

Delaying treatment for patients with severe hyponatremia with the risk of severe brain injury of death should be avoided. The ESE guidelines are conservative and avoid the trap of delaying treatment while trying to choose between fluid restriction or fluid administration. Fluid restriction, diuretics or the use of salt tablets have no use in the immediate treatment of a critically ill patient with severe hyponatremia of uncertain cause.

## REFERENCES

1. Peters JP, Welt LG, Sims EA, Orloff J, Needham J. A salt-wasting syndrome associated with cerebral disease. Trans Assoc Am Physicians. 1950:63:57-64.
2. Schwartz, William B.; Bennett, Warren; Curelop, Sidney; Bartter, Frederic C. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am J Med. 1957;23(4):529-42.
3. Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. Am J Med. 1967;42(5):790-806.
4. Nelson PB, Seif SM, Maroon JC, Robinson AG. Hyponatremia in neurosurgical patients: a syndrome of cerebral salt wasting Journal of Neurosurgery. 1981;55(6):938-94
5. Ohta M, Ito S. [Hyponatremia and inflammation]. Rinsho Byori. Rinsho Byori. 1999;47(5):408-16.

6. Gionis D, Ilias I, Moustaki M, Mantzos E, Papadatos I, Koutras DA, Mastorakos G. Hypothalamic-pituitary-adrenal axis and interleukin-6 activity in children with head trauma and syndrome of inappropriate secretion of antidiuretic hormone. J Pediatr Endocrinol Metab. 200;16(1):49-54.
7. Yildirim C, Kekec Z, Sozuer EM, Ikizceli I, Avsarogullari L. Blood levels of acute phase reactants with traffic accidents. Soud Lek. 2004;49(2):25-9.
8. Lim GW, Lee M, Kim HS, Hong YM, Sohn S. Hyponatremia and syndrome of inappropriate antidiuretic hormone secretion in Kawasaki disease. Korean Circ J. 2010;40(10):507-13.
9. Mastorakos G, Weber JS, Magiakou MA, Gunn H, Chrousos GP. Hypothalamic-pituitary-adrenal axis activation and stimulation of systemic vasopressin secretion by recombinant interleukin-6 in humans: potential implications for the syndrome of inappropriate vasopressin secretion. J Clin Endocrinol Metab. 1994;79(4):934-9.
10. Hodax JK, Bialo SR, Yalcindag A. SIADH in Systemic JIA Resolving After Treatment With an IL-6 Inhibitor. Pediatrics. 2018;141(1):e20164174.
11. Park SJ, Shin JI. Inflammation and hyponatremia: an underrecognized condition? Korean J Pediatr. 2013;56(12):519-22.
12. Schwartz, William B.; Bennett, Warren; Curelop, Sidney; Bartter, Frederic. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am J Med . 1957;23(4):529-42.
13. Maesaka JK, Imbriano LJ, Miyawaki N. Determining Fractional Urate Excretion Rates in Hyponatremic Conditions and Improved Methods to Distinguish Cerebral/Renal Salt Wasting From the Syndrome of Inappropriate Secretion of Antidiuretic Hormone. Front Med (Lausanne). 2018;5:319.
14. Maesaka JK, Venkatesan J, Piccione JM, Decker R, Dreisbach AW, Wetherington J. Plasma natriuretic factor(s) in patients with intracranial disease, renal salt wasting and hyperuricosuria. Life Sci. 1993;52(23):1875-82.
15. Maesaka JK, Imbriano LJ, Pinkhasov A, Muralidharan R, Song X, Russo LM, Comper WD. Identification of a Novel Natriuretic Protein in Patients With Cerebral-Renal Salt Wasting-Implications for Enhanced Diagnosis. Am J Med Sci. 2021;361(2):261-268.
16. Maesaka JK, Imbriano LJ, Miyawaki N. High Prevalence of Renal Salt Wasting Without Cerebral Disease as Cause of Hyponatremia in General Medical Wards. Am J Med Sci. 2018;356(1):15-22.
17. Maesaka JK, Imbriano LJ, Pinkhasov A, Muralidharan R, Song X, Russo LM, Comper WD. Identification of a Novel Natriuretic Protein in Patients With Cerebral-Renal Salt Wasting-Implications for Enhanced Diagnosis. Am J Med Sci. 2021;361(2):261-268.
18. Pourmand A, Pyle M, Yamane D, Sumon K, Frasure SE. The utility of point-of-care ultrasound in the assessment of volume status in acute and critically ill patients. World J Emerg Med. 2019;10(4):232-238.

19. Misango D, Pattnaik R, Baker T, Dünser MW, Dondorp AM, Schultz MJ. Hemodynamic Assessment and Support in Sepsis and Septic Shock in Resource-Limited Settings. 2019 Feb 9. In: Dondorp AM, Dünser MW, Schultz MJ, editors. Sepsis Management in Resource-limited Settings [Internet]. Cham (CH): Springer; 2019. Chapter 7.
20. Chung HM, Kluge R, Schrier RW, Anderson RJ. Clinical assessment of extracellular fluid volume in hyponatremia. Am J Med. 1987;83(5):905-8.
21. Kim GH. Pathophysiology of Drug-Induced Hyponatremia. J Clin Med. 2022;11(19):5810.
22. Iovino M, Iacoviello M, De Pergola G, Licchelli B, Iovino E, Guastamacchia E, Giagulli VA, Triggiani V. Vasopressin in Heart Failure. Endocr Metab Immune DisordDrugTargets. 2018;18(5):458-465.
23. Catalano A, Basile G, Ferro C, et al. : Hyponatremia as a leading sign of hypopituitarism. Journal of Clinical and Translational Endocrinology: case reports. 2017.
24. Rondon-Berrios H, Velez JCQ. Hyponatremia in Cirrhosis. Clin Liver Dis. 2022;26(2):149-164.
25. Martin-Grace J, Dineen R, Sherlock M, Thompson CJ. Adrenal insufficiency: Physiology, clinical presentation and diagnostic challenges. Clin Chim Acta. 2020;505:78-91.
26. Refardt J, Imber C, Sailer CO, Jeanloz N, Potasso L, Kutz A, et al. A Randomized Trial of Empagliflozin to Increase Plasma Sodium Levels in Patients with the Syndrome of Inappropriate Antidiuresis. J Am Soc Nephrol. 2020;31(3):615-624.
27. Miell J, Dhanjal P, Jamookeeah C. Evidence for the use of demeclocycline in the treatment of hyponatraemia secondary to SIADH: a systematic review. Int J Clin Pract. 2015;69(12):1396-417.
28. Rondon-Berrios H. Urea for Chronic Hyponatremia. Blood Purif. 2020;49(12):212-218.
29. Li N, Zhang H, Wang S, Xu Y, Ying Y, Li J, et al. Urea transporter UT-A1 as a novel drug target for hyponatremia. FASEB J. 2024;38(13):e23760.
30. Berl T, Quittnat-Pelletier F, Verbalis JG, Schrier RW, Bichet DG, Ouyang J, Czerwiec FS; SALTWATER Investigators. Oral tolvaptan is safe and effective in chronic hyponatremia. J Am Soc Nephrol. 2010;21(4):705-12.
31. Mount DB. Thick ascending limb of the loop of Henle. Clin J Am Soc Nephrol. 2014;9(11):1974-86.
32. Lee JJ. Cerebral Salt Wasting Syndrome Associated with Status Epilepticus. J Epilepsy Res. 2022;12(2):82-84.
33. Sudha Garimella, Sasigarn A Bowden, James E. Springate. Cerebral Salt-wasting Syndrome, Medscape. Aug. 19, 2024.
34. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, Thompson CJ. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013;126(10 Suppl 1):S1-42.

35. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet De, t al; Hyponatraemia Guideline Development Group. Clinical practice guideline on diagnosis and treatment of hyponatremia. Eur J Endocrinol. 2014;170(3):G1-47.
36. Verbalis J. How to manage hyponatraemia according to guidelines? The USA perspective. In Endocrine Abstracts, 2015, vol 37; D1.2 of European Society of Endocrinology.
37. Marco Avila. The Clinical Practice Guideline on diagnosis and treatment of hyponatraemia: a response from Otsuka Pharmaceutical Europe Ltd. Eur J Endocrinol . 2014;171(1):L1-3.
38. Garrahy A, Cuesta M, Murphy B, O'Reilly MW, Tormey WP, Sherlock M, Thompson CJ. Active management of severe hyponatraemia is associated with improved mortality. Eur J Endocrinol. 2021;184(1):9-17.
39. Sterns RH, Nigwekar SU, Hix JK. The treatment of hyponatremia. Semin Nephrol. 2009;29(3):282-99.
40. Beck J, Arshad MF, Iqbal A, Christ-Crain M. Severe symptomatic hyponatremia in Europe: insights into current clinical practice. Eur J Endocrinol. 2025;192(6):754-762.
41. MacMillan TE, Shin S, Topf J, Kwan JL, Weinerman A, Tang T, Raissi A, Koppula R, Razak F, Verma AA, Fralick M. Osmotic Demyelination Syndrome in Patients Hospitalized with Hyponatremia. NEJM Evid. 2023;2(4):EVIDoa2200215.
42. Falhammar H, Andersson Franko M, Lindh JD, Skov J, Mannheimer B. Neurologic and psychiatric disorders following correction of profound hyponatremia - A cohort study. Eur J Intern Med. 2025;140:106394.