CSWS Versus SIADH as the Probable Causes of Hyponatremia in Children With Acute CNS Disorders

How to Cite This Article: Sorkhi H, Salehi Omran MR, Barari Savadkoohi R, Baghdadi F, Nakhjavani N, Bijani A. CSWS versus SIADH as the probable Causes of Hyponatremia in Children with Acute CNS Disorders. Iran J Child Neurol. 2013 Summer; 7(3): 34-39.

Abstract
Objective
There is a major problem about the incidence, diagnosis, and differentiation of cerebral salt wasting syndrome (CSWS) and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in patients with acute central nervous system (CNS) disorders. According to rare reports of these cases, this study was performed in children with acute CNS disorders for diagnosis of CSWS versus SIADH.

Materials & Methods
This prospective study was done on children with acute CNS disorders. The definition of CSWS was hyponatremia (serum sodium ≤130 mEq/L), urine volume output ≥3 ml/kg/hr, urine specific gravity ≥1020 and urinary sodium concentration ≥100 mEq/L. Also, patients with hyponatremia (serum sodium ≤130 mEq/L), urine output < 3 ml/kg/hr, urine specific gravity ≥1020, and urinary sodium concentration >20 mEq/L were considered to have SIADH.

Results
Out of 102 patients with acute CNS disorders, 62 (60.8%) children were male with mean age of 60.47±42.39 months. Among nine children with hyponatremia (serum sodium ≥130 mEq/L), 4 children had CSWS and 3 patients had SIADH. In 2 cases, the cause of hyponatremia was not determined. The mean day of hyponatremia after admission was 5.11±3.31 days. It was 5.25±2.75 and 5.66±7.23 days in children with CSWS and SIADH, respectively. Also, the urine sodium (mEq/L) was 190.5±73.3 and 58.7±43.8 in patients with CSWS and SIADH, respectively.

Conclusion
According to the results of this study, the incidence of CSWS was more than SIADH in children with acute CNS disorders. So, more attention is needed to differentiate CSWS versus SIADH in order to their different management.

Keywords: Children; Acute CNS disorders; Cerebral salt wasting; Syndrome of inappropriate secretion of ADH

Introduction
The concept of cerebral salt wasting syndrome (CSWS) was abandoned for a long time, despite it had been reported seven years before the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (1950 versus 1957)
Hyponatremia is a common problem in central nervous system (CNS) disorders, and usually was attributed to SIADH (3-6). The main danger of hyponatremia is swelling of brain cells and increase of intracellular fluid (7-9). Therefore, early diagnosis and appropriate management, especially in children with acute neurologic disorders are of great importance. In SIADH, hyponatremia is caused by water retention due to inappropriate secretion of antidiuretic hormone (ADH) (10-15). But in CSWS, hyponatremia is associated with high urine output, high urine sodium concentration, and plasma volume depletion (16).

It is a major problem to distinguish CSWS from SIADH. Also, early diagnosis of them is very important, because SIADH is associated with volume retention, therefore, water restriction is the essential concept of their management (17,18). But CSWS is caused by the release of natriuretic peptides and hypovolemic hyponatremia that are associated with high urine volume and natriuresis. So, replacement of fluid and correction of hyponatremia are more important in CSWS (19).

Although subarachnoid hemorrhage (SAH) is one the most common cause of CSWS (4), other acute CNS disorders, such as septic, viral, and herpetic meningitis have been reported as causes of CSWS (20-23). There are rare reports of the incidence of hyponatremia in children with acute CNS disorders and also about SIADH versus CSWS. Moreover, SIADH may be more considered than CSWS and the diagnosis of CSWS is frequently missed by neurologists. So, this study was done on children with acute CNS disorders referred to Amirkola children hospital, Babol, Iran, with the aim of diagnosis of CSWS versus SIADH.

Materials & Methods
In this prospective study, all children with acute CNS disorders who were admitted to Amirkola Children Hospital (from May 2010 to November 2011) were enrolled in the study.

Acute CNS disorders were as follows:
1. Status epileptics: convulsion more than 30 minutes;
2. Encephalopathy: the existence of at least two of the following symptoms that are presented by altered level of consciousness, cognition, personality, or seizures;
3. Encephalitis: encephalopathy and cerebral spinal fluid (CSF) pleocytosis;
4. Altered level of consciousness: increase or decrease of neuronal excitability that progress to coma;
5. Traumatic brain injury;
6. Aseptic meningitis: sign of meningismus and CSF leukocytosis without bacterial or fungal infection;
7. Septic meningitis: sign of meningismus and CSF leukocytosis with bacterial or fungal infection.

The definition of CSWS was hyponatremia (serum sodium ≤130 mEq/L), urine output ≥3 ml/kg/hr, urine specific gravity ≥1020, and urinary sodium ≥100 mEq/L (16). Also, patients with hyponatremia (serum sodium ≤130 mEq/L) according to every day serum sampling, urine output < 3 ml/kg/hr, urine specific gravity ≤1020, and urinary sodium concentration > 20 mEq/lit were considered to have SIADH (11).

The exclusion criteria were as follows: all patients with history of endocrine, metabolic, renal or chronic neurologic disorders, and use of diuretic or manitol. The data were analyzed by t-test using SPSS software. p<0.05 was considered statistically significant.

Results
In this study, 102 patients with acute CNS disorders were included. Sixty-two (60.8%) patients were males and 40 (39.2%) were females.

Among these patients, 9 (8.8%, CI95%: 3.22-13.32%) children had hyponatremia (serum sodium <130 mEq/L). Four (3.92%, CI95%: 0.09-7.75%) had CSWS and 3 (2.9%, CI95%: 0.01- 6.28%) had SIADH. Also, 2 children had unknown cause of hyponatremia.

The mean age of patients was 93.40±40.31 months in children with CSWS and 96±43.26 months in patients with SIADH.

The mean age of patients was 60.37±42.39 months (2-168 months). This was 93.40±40.31 months in children with CSWS and 96±43.26 months in patients with SIADH.

The most common causes of admission in children with acute CNS disorders were septic meningitis (31.4%) and traumatic brain injury (19.6%) (Table 1). The mean serum level of sodium in all patients was 137±5.49 mEq/L (112-146 mEq/L). In patients with hyponatremia, the mean serum level of sodium was 124.7±5.9 mEq/L. It was 124.1±8.2 mEq/L in children with CSWS, and 124.8±4.5 mEq/L in patients with SIADH.
The causes of hyponatremia in CNS disorders and especially after neurosurgery are different and may be related to over administration of hypotonic fluid, use of diuretic, SIADH, CSWS, hypothyroidism, as well as renal, liver, or adrenal insufficiently (19). It is very important to differentiate the causes of hyponatremia (especially SIADH versus CSWS), because there are different management for them (19,31,32).

Both disorders have high urine osmolality and increase of specific gravity, but in SIADH, it is due to inappropriate secretion of antidiuretic hormone (ADH), and in CSWS is associated with volume contraction. Also, urinary sodium loss is high in both disorders, but it is higher in CSWS (32).

The most important finding for differentiation of CSWS from SIADH is decrease in blood volume (hypotension, decreased skin turgor, and increased hematocrite) with high urine sodium concentration. However, patients with SIADH may have normal or mild increase in blood volume (13,27).

The pathogenesis of CSWS is not clear. Some important factors are: arterial natriuretic peptide (ANP), brain natriuretic factor (BNP), C-type natriuretic factor (CNP) and dendroaspis natriuretic peptide (DNP), but the role of BNP is more important (33-37). Also, in spite of increase in natriuretic peptides, other mechanisms may be important for pathogenesis of CSWS, such as abnormality of sympathetic nervous system and increase in natriuresis (19).

The different incidence of CSWS versus SIADH in patient with acute neurologic disorder may be due to different criteria for differentiation of CSWS and SIADH. For example, in some studies, the definition of hyponatremia was “serum sodium ≤ of 135 mEq/L,” and in some others, it was serum sodium ≤130 mEq/L. In one study, the definition of CSWS was negative blood volume balance more than 20%, or increase of hematocrite without administration of transfusion, and in another study, urinary sodium concentration more than 120 mEq/L, urinary osmolality more than 300 mOsm/kg H₂O, urine volume more than 2-3 ml/kg/hr were criteria for CSWS. In one study, fraction excretion of uric acid more than 10% with natriuresis and decrease of blood volume were used for definition of CSWS and in

**Discussion**

According to the findings of this study, 9 (55%) patients with acute CNS disorders had hyponatremia, and CSWS cases were more than SIADH. In Bussmann et al. study that was done on 195 children with acute CNS disorders for 5 years, 20 (10.3%) children had hyponatremia (serum sodium level ≤130 mEq/L); 9 (4.5%) children had CSWS; and 7 (3.5%) had SIADH. Therefore, the rate of CSWS was more than SIADH (24). Jimenez reported 14 (1.13%) children with CSWS in 1229 patients (less than 15 years old) after neurosurgery and after admission to pediatric intensive care unit (PICU) (16). In other study on 282 children (291 neurosurgery patients due to brain tumors), CSWS was detected in 15 (5%) cases, and 9 (3%) patients had SIADH (25). Although, in Agha et al.’s study that was done on 316 patients with subarachnoid hemorrhage (SAH), 179 (56.6%) patients had hyponatremia (serum sodium level ≤135 mEq/L). The causes of hyponatremia were SIADH and CSWS in 39 (62.9%) and 4 (6.5%) patients, respectively (26). However, there are many studies that were recommended CSWS does not really exist and these patients may be in SIADH category (11,27,28). For example, in a study performed on 40 patients with hyponatremia and suspected SIADH or CSWS (in ICU), there were not any cases with diagnosis of CSWS (11). Also, Singh et al. reported that CSWS is very rare and less common than SIADH (29). But there are some studies that reported CSWS may be more common than SIADH in patients with SAH and intracranial infection (encephalitis, meningitis (20-23,30).
another study, increase in urinary sodium and chloride excretion were used for definition of CSWS. Also, central venous pressure (CVP) was used for determination of blood volume (16,20,24,38,39).

In spite of different definition of CSWS, the existence of CSWS (even more than SIADH) in our study indicated the importance of early diagnosis and making a good plan for its management.

Among 9 Children with hyponatremia, 3 (30%) patients had status epilepticus, that 2 cases had CSWS and one had SIADH. In Jiménez et al.’s study, brain tumor was the most common causes of hyponatremia (16). SAH was the most common cause of hyponatremia in Bussmann et al.’s report and the majority of their patients with CSWS had neurosurgery operation for brain tumor (24). Our hospital is a referral children hospital and the majority of patients have non-surgical problem. Therefore, the difference in incidence and cause of hyponatremia may be due to our different referral patients.

In our study, 5 patients with hyponatremia were female and in 2 patients with hyponatremia the cause was unknown. Among 16 patients with hyponatremia and diagnosis of CSWS or SIADH, 8 patients were female (24). In another study, 9 children with hyponatremia and acute CNS disorders were males and 6 patients were female (16). Therefore, it seems that the risk of hyponatremia is not different between two sexes.

In conclusion, in summary, there is a risk of hyponatremia in different disorders of acute CNS diseases. Although there were small numbers of both CSWS and SIADH patients, but the risk of CSWS is more than SIADH in children with acute neurologic disorders. So, according to different managements of these disorders, more attention is needed for differentiation of CSWS versus SIADH.

Table 1. Frequency of Primary Acute CNS Disorders in Children Who Referred to Amirkola Children Hospital

| Primary disease           | Frequency |
|--------------------------|-----------|
| Status epilepticus       | 9 (8.8%)  |
| Encephalitis             | 4(3.9%)   |
| Encephalopathy           | 17(16.7%) |
| Altered level of Consciousness | 6 (5.9%) |
| Traumatic brain injury   | 20(19.6%) |
| Aseptic meningitis       | 14(13.7%) |
| Septic meningitis        | 32(31.4%) |
| Total                    | 102       |

Table 2. Characteristics of Patients With Hyponatremia in Children with Acute CNS Disorders Referred to Amirkola Children Hospital According to Diagnosis

| Age (Months) | Sex  | Primary disorders          | Serum Na level | Days of hyponatremia | Final diagnosis of hyponatremia |
|--------------|------|----------------------------|----------------|----------------------|---------------------------------|
| 2.5          | Male | Head Trauma                | 122            | 1                    | Unknown                        |
| 60           | Female | Septic meningitis         | 128            | 14                   | ASIDH                          |
| 62           | Male  | Head Trauma                | 129            | 7                    | CSWS                           |
| 144          | Female | Status epilepticus        | 123.2          | 1                    | SIADH                          |
| 84           | Female | Intracranial hemorrhage    | 125.5          | 2                    | SIADH                          |
| 120          | Male  | Encephalopathy             | 129.7          | 7                    | Unknown                        |
| 60           | Male  | Status epilepticus        | 129            | 4                    | CSWS                           |
| 144          | Female | Status epilepticus        | 127            | 2                    | CSWS                           |
| 108          | Female | Intracranial hemorrhage    | 112            | 8                    | CSWS                           |
### Table 3. Laboratory Characteristics of Children with Acute CNS Disorders with Hyponatremia (CSWS and SIADH) Referred to Amirkola Children Hospital

| Characteristics                  | CSWS Mean±SD | SIDAH Mean±SD |
|----------------------------------|--------------|---------------|
| Serum Sodium (mEq/lit)           | 124.1± 8.2   | 124.8± 4.5    |
| Urine Specify gravity            | 1025/75 ± 4.19 | 1024.66± 7.57 |
| Serum Osmolallity (mOsmol/kg H2O) | 247.15±15.62  | 246± 4.21     |
| Urine Volume (ml/kg/hr)          | 4.24±1.44    | 2.77± 0.32    |
| Urine Sodium (mEq/lit)           | 190.5±73.3   | 58.7± 43.8*   |
| Serum Uric Acid (mg/dl)          | 1.25±0.07    | 4.43±2.45     |
| Serum Creatinine (mg/dl)         | 0.55 ± 0.12  | 0.64±0.05     |
| Serum Potassium (mEq/L)          | 3.86±0.94    | 3.83±0.97     |

*p<0.05

### References

1. Peters JP, Welt LG, Sims EAH. A salt wasting syndrome associated with cerebral disease. Trans Assoc Am Physicians 1957;63:57-64.
2. Schwartz WB, Bennett W, Curelop S. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am J Med 1950;23(4); 529-42.
3. Hasan D, Wijdicks EF, Vermeulen M. Hyponatremia is associated with cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage. Ann Neurol 1990;27(1):106-8.
4. Sherlock M, O’Sullivan E, Agha A, Behan LA, Rawluk D, Brennan P, et al. The incidence and pathophysiology of hyponatremia after subarachnoid haemorrhage. Clin Endocrinol (Oxf). 2006;64(3):250-4.
5. Wartenberg KE, Schmidt JM, Claassen J, Temes RE, Frontera JA, Ostapkovich N, et al. Impact of medical complications on outcome after subarachnoid hemorrhage. Crit Care Med 2006;34(3):617-23; quiz 624.
6. Qureshi AI, Suri MF, Sung GY, Straw RN, Yahia AM, Saad M, et al. Prognostic significance of hypernatremia and hyponatremia among patients with aneurysmal subarachnoid hemorrhage. Neurosurgery 2002;50(4):749-55.
7. Bianchetti MG, Simonetti GD, Bettinelli A. Body fluids and salt metabolism - Part I. Ital J Pediatr 2009;15(1):36.
8. Peruzzo M, Milani GP, Garzoni L, Longoni L, Simonetti GD, Bettinelli A, et al. Body fluids and salt metabolism - part II. Ital J Pediatr 2010;36(1):78.
9. Moritz ML, Ayus JC. New aspects in the pathogenesis, prevention, and treatment of hyponatremic encephalopathy in children. Pediatr Nephrol. 2010;25(7):1225-38.
10. Albanese A, Hindmarsh P, Stanhope R. Management of hyponatraemia in patients with acute cerebral insults. Arch Dis Child 2001;85(3):246-51.
11. Brimioulle S, Orellana-Jimenez C, Aminian A, Vincent JL. Hyponatremia in neurological patients: cerebral salt wasting versus inappropriate antidiuretic hormone secretion. Intensive Care Med 2008;34(1):125-31.
12. Yee AH, Burns JD, Wijdicks EF. Cerebral salt wasting: pathophysiology, diagnosis, and treatment. Neurosurg Clin N Am 2010;21(2):339-52.
13. Palmer BF. Hyponatremia in a neurosurgical patient: syndrome of inappropriate antidiuretic hormone secretion versus cerebral salt wasting. Nephrol Dial Transplant 2000;15(2):262-8.
14. Rivkees SA. Differentiation appropriate antidiuretic hormone secretion, inappropriate antidiuretic secretion...
and cerebral salt wasting: the common, uncommon, and misnamed. Curr Opin Pediatr 2008;20(4):448-52.

15. Sterns RH, Silver SM. Cerebral salt wasting versus SIADH: What difference? J Am Soc Nephrol 2008;19(2):194-6.

16. Jiménez R, Casado-Flores J, Nieto M, Garcia-Teresa MA. Cerebral salt wasting syndrome in children with acute central nervous system injury. Pediatr Neurol 2006;35(4):261-3.

17. Bartter FC, Schwartz WB. Syndrome of inappropriate secretion of antidiuretic hormone. Am J Med 1967;42:790-806.

18. Verbalis JG. Pathogenesis of hyponatremia in an experimental model of the syndrome of inappropriate antidiuresis. Am J Physiol 1994;267(6 Pt 2):R1617-25.

19. Harrigan MR. Cerebral salt wasting syndrome: a review. Neurosurgery 1996;38(1):152-60.

20. Inatomi J, Yokoyama Y, Sekine T, Igarashi T. A case of cerebral salt-wasting syndrome associated with aseptic meningitis in an 8-year-old boy. Pediatr Neurol 2008;23(4):659-62.

21. Brookes MJ, Gould TH. Cerebral salt wasting syndrome in meningoencephalitis: a case report. J Neurol Neurosurg Psychiatry 2003;74(2):277.

22. Cuadrado-Godia E, Cerda M, Rodriguez-Campello A, Puig de Dou J. Síndrome pierde sal cerebral en las infecciones del sistema nervioso central. Med Clin (Brc) 2007;24:128(7);229-9.

23. Roca-Ribas F, Ninno JE, Gasperin A, Lucas M, Liubia C. Cerebral salt wasting syndrome as a postoperative complication after surgical resection of acoustic neuroma. Otol Neurotol 2002;23:992-3.

24. Bussmann C, Bast T, Rating D. Hyponatraemia in children with acute CNS disease: SIADH or cerebral salt wasting? Childs Nerv Syst 2001;17(1-2):58-62.

25. Hardesty DA, Kilbaugh TJ, Storm PB. Cerebral Salt Wasting Syndrome in Post-Operative Pediatric Brain Tumor Patients. Neurocrit Care 2012;17(3):382-7.

26. Agha A, Thornton E, O’Kelly P, Tormey W, Phillips J, Thompson CJ. Posterior pituitary dysfunction after traumatic brain injury. J Clin Endocrinol Metab 2004;89(12):5987-92.

27. Singh S, Bohn D, Carlotti AP, Cusimano M, Rutka JT, Halperin ML. Cerebral salt wasting: truths, fallacies, theories, and challenges. Crit Care Med. 2002 Nov;30(11):2575-9.

28. Carlotti AP, Bohn D, Rutka JT, Singh S, Berry WA, Sharman A, et al. A method to estimate urinary electrolyte excretion in patients at risk for developing cerebral salt wasting. J Neurosurg 2001;95(3):420-4.

29. International committee for Standardization in Haematology. Recommended methods for measurement of red-cell and plasma volume. J Nucl Med 1980;21(8):793-800.

30. Byeon JH, Yoo G. Cerebral salt wasting syndrome after calvarial remodeling in craniosynostosis. J Korean Med Sci 2005;20(5):866-9.

31. Gutierrez OM, Lin HY. Refractory hyponatremia. Kidney Int 2007;71(1):79-82.

32. Maesaka JK, Imbriano LJ, Al-NM, Illamathi E. Is it cerebral or renal salt wasting? Kidney Int 2009;76(9):934-8.

33. Maesaka JK, Venkatesan J, Piccione JM, Decker R, Dreischaw AW, Wetherington JD. Abnormal urate transport in patients with intracranial disease. Am J Kidney Dis 1992;19(1):10-5.

34. Berendes E, Walter M, Cullen P, Prien T, Van Aken H, Horstemke J, et al. Secretion of brain natriuretic peptide in patients with aneurysmal subarachnoid haemorrhage. Lancet 1997 Jan 25;349(9047):245-9.

35. Kurokawa Y, Uede T, Ishiguro M, Honda O, Honmou O, Kato T, et al. Pathogenesis of hyponatremia following subarachnoid hemorrhage due to ruptured cerebral aneurysm. Surg Neurol 1996;46(5):500-7.

36. Khurana VG, Wijdicks EF, Heublein DM, McClelland RL, Meyer FB, Piepgras DG, et al. A pilot study of dendraospis natriuretic peptide in aneurysmal subarachnoid hemorrhage. Neurosurgery 2004;55(1):69-75.

37. Kaneko T, Shirakami G, Nakao K, Nagata I, Nakagawa O, Hama N, et al. C-type natriuretic peptide (CNP) is the major natriuretic peptide in human cerebrospinal fluid. Brain Res 1993;612(1-2):104-9.

38. Damaraju SC, Rajshkekar V, Chandy MJ. Validation study of a central venous pressure-based protocol for the management of neurosurgical patients with hyponatremia and natriuresis. Neurosurgery 1997;40(2):312-6.

39. Sivakumar V, Rajshkekar V, Chandy MJ. Management of neurosurgical patients with hyponatremia and natriuresis. Neurosurgery 1994;34(2):269-74; discussion 274.