Incidence and Predictors of Cerebral Salt Wasting Syndrome in Stroke Patients – Results of a Prospective Observational Study

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Research Article

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Abstract

Background

Cerebral salt wasting syndrome (CSWS) and Syndrome of Inappropriate Anti Diuretic Hormone secretion (SIADH) are the most common aetiological factors for developing hyponatremia following stroke. The differentiation of these two entities is crucial as the treatment options are completely different. Hence the knowledge on predictors of CSWS is important to make a more accurate diagnosis of CSWS.

Methods

Two hundred and fourty six patients with confirmed stroke were prospectively observed throughout the hospital stay in a tertiary referral center in Sri Lanka to identify the possible predictors of CSWS. Hyponatremia was defined as serum Na^+ level less than 131mmo/l. Serum osmolality, urine osmolality, urinary Na^+, serum cortisol and thyroid function tests were performed on all the hyponatremic patients. Differentiation of the CSWS and SIADH was based on physical examination findings and laboratory parameters.

Results

The incidence of hyponatremia in our study population was 19.1% (95% Confidence Interval 14.39-24.58). The majority of patients (24, 51%) were attributed to CSWS. SIADH group comprised of 17 (36.2%) patients and 6 (12.7%) patients had other undetermined causes. There was a significant statistical difference between the aetiologies of hyponatremia and laboratory investigations like urinary Na^+, urinary osmolality and serum osmolality. Demographic characteristics, comorbidities, imaging findings and clinical parameters like systolic blood pressure, diastolic blood pressure, on admission GCS were considered in the multivariable logistic regression model and the overall model was not significant.

Conclusion

The incidence of CSWS is higher than the incidence of SIADH. The demographic characteristics, comorbidities, imaging and clinical parameters like blood pressure, on admission GCS could not predict the occurrence of CSWS

1. Background

Hyponatremia is a common and important electrolyte abnormality seen in critically ill neurosurgical patients. Even though there are many aetiologies for hyponatremia, Syndrome of Inappropriate Anti Diuretic Hormone secretion (SIADH) and Cerebral Salt Wasting Syndrome (CSWS) are the main aetiological factors in neurological patients (1).

In SIADH, inappropriate release of vasopressin occurs which results in dilutional hyponatremia. In contrast, primary natriuresis along with depletion of extravascular volume is seen in CSWS (2). Reduced

sympathetic neural input to the kidney and natriuretic peptide theory are two suggested theories for the occurrence of CSWS (3).

As both disorders can occur in intracranial pathologies and share same clinical and biochemical parameters, it is difficult to differentiate one from the other (4). The hallmark of differentiating these two entities lies in the extravascular volume status. In SIADH, the extravascular volume is normal or slightly high comparing to the low volume seen in CSWS. However the accurate determination of extravascular volume status is an absolutely a difficult task (5). Therefore, both clinical and biochemical data should be considered cumulatively to arrive at an accurate diagnosis of hypovolemia (6). Clinical signs of hypovolemia mainly include dry mucous membranes, increased skin turgor, sunken eyes and orthostatic hypotension. Biochemically there is elevated levels of hematocrit, s.albumin, blood urea nitrogen and s.creatinine values which indicate the presence of hypovolemia. In patients who are monitored in intensive care units, low pulmonary capillary pressure or low central venous pressure indicate the low circulating extravascular volume (6, 7). However assessing the serum levels of antidiuretic hormone or natriuretic peptides will not help to differentiate these two disorders (6).

Differentiating these two disorders is of utmost importance as they have different management approaches. Fluid restriction is indicated in uncomplicated SIADH. Isotonic saline is not recommended as it could further worsen the hyponatremia by retaining more water. The effect of using hypertonic saline is also not long lasting. Therefore, the use of diuretics and new class of drugs called vaptans are recommended in SIADH management (8).In contrast, replacing water is the first line management approach in CSWS. Isotonic saline is used and this would solve both hypovolemia and hyponatremia. If the condition is severe, hypertonic saline is recommended for the resuscitation (9). However, the correction of hyponatremia should be carried out with caution to prevent complications like osmotic demyelination syndrome (10). Previous literature provides evidence to suggest the importance of using mineralocorticoids in CSWS as they are potent in reabsorbing Na^+ form distal collecting tubules of the nephron (9).

The importance of differentiating these two disorders is obvious as they have totally different management approaches. Therefore it is important to study about parameters which could predict CSWS. Previous studies have investigated about the ability of haptoglobin gene and aneurysm location of sub arachnoid haemorrhage patients in predicting CSWS (11, 12). The purpose of this study is to investigate whether demographic data, past medical history, imaging parameters and some of the clinical parameters of stroke patients could predict the occurrence of CSWS.

2. Methodology

2.1 Design and Setting

A prospective cohort study was carried out on 246 stroke patients admitted to Teaching hospital Peradeniya located in the central province of Sri Lanka. The sample size calculation was based on the

previously reported prevalence of hyponatremia of 20% due to intracerebral events(13). The following statistical formula was used to calculate the sample size.

$n = Z^2 P (1 - P) / d^2$

n = Sample Size

Z = The statistic corresponding to level of confidence. This value is 1.96 if α = 5%

P = Estimated prevalence of hyponatremia among stroke patients in hospital setting

d = Maximum acceptable error 5%

Ethical clearance to this study was obtained from the Ethics Review Committee, Faculty of Medicine, University of Peradeniya, Sri Lanka (2018/EC/44). Written informed consent was obtained from the patient or, in the instances where the patient was not clinically fit to do so, from the next of kin.

2.2 Data collection

The current paper is based on the data from patients of stroke recruited prospectively from 1st of June 2019 to 12th of February 2021. The diagnosis of stroke was established on the clinical history, examination and neuroimaging. Hyponatremia was defined as serum Na^+ level less than 131mmo/l (14). Patients with known pre-event hyponatremia were excluded from the study. All the patients with low Na^+ levels were assessed for their serum osmolality levels. The patients with low S. osmolality (<285mosm/Kg) levels were further tested for their urine osmolality level. Those patients of high urine osmolality levels were assessed for their volume status. Moreover these patients were assessed for T4/TSH (Thyroid Stimulating Hormone) levels and S.Cortisol levels to exclude hypothyroidism and adrenal insufficiency respectively. The differentiation of the CSWS and SIADH was based on clinical examination findings, urinary Na^+ values and hematocrit values. CSWS was diagnosed if there was clinically declared dehydration, urinary Na^+ value > 50mEq/L and elevated or normal hematocrit value. In contrast, SIADH was diagnosed if there was absence of clinical dehydration, urinary Na^+ value 20-50mEq/L and reduced or normal hematocrit value.

2.3 Statistical analysis

Descriptive statistics were calculated as means, standard deviations and percentages. Fisher's exact test or Pearson chi square test for categorical variables and Kruskal-Wallis test for continuous variables were used to compare the demographic, clinical, laboratory and imaging parameters with CSWS and SIADH groups. Incidence of hyponatremia and its 95% confidence intervals (CI) were calculated. Multivariate logistic regression analysis was performed to evaluate the predictors of CSWS. A P value of 0.05 or less than that is considered to be significant. The data analysis was done by using STATA version 16 (StataCorp. 2019. *Stata Statistical Software*:College Station, TX: StataCorp LLC.).

3. Results

3.1 Study participant characteristics

The study sample comprised of 246 proven cases of stroke patients. The mean age of the study participants was 68.14 years (SD ± 12.71). The percentage of male was 48.7% and the mean age was 68.25 years (SD ± 12.25). The mean age of the females was 67.8 years (SD ± 12.65) and there was no statistical difference between age of males and females (P = 0.778). Most of the patients (57.32%) belonged to the age group of 60-79 years. Among the study group, 27.2% were smokers and 64.3% were non-alcoholics.

In the study sample, 56.09% patients were on treatment for hypertension. However there was 21.1% patients who were not diagnosed previously, but having high blood pressure on admission and 28.8% of hypertensive patients had uncontrolled hypertension while on treatment. Of all the hypertensive patients, 52.5% were on lipid lowering drugs. Of the study sample, diabetes mellitus comprised of 30.8% of patients and 13% of patients were on lipid lowering drugs.

Of the 246 stroke patients, 79.7% had ischaemic stroke and 20.3% had haemorrhagic stroke. In the stroke patients' sample the prevalence of left sided stroke was 39.02%, 41.8% had right sided stroke and 19.1% had bilateral strokes.

3.2 Evaluation of hyponatremia

Out of 246 stroke patients, 47 patients (19.1%) developed hyponatremia (95% CI 14.39-24.58). The majority of patients (24, 51%) were attributed to CSWS. There were 4 patients who had low hematocrit value <37 with urinary Na^+ > 100mEq/L and those patients were considered to be CSWS as their renal salt wasting was significantly high, even though the hematocrit value was not suggestive of CSWS. SIADH group comprised of 17 (36.2%) patients and 6 (12.7%) patients had other undetermined causes. The mean day of development of hyponatremia was 1.81days (SD ± 1.73) and there was no statistical difference between CSWS, SIADH and Other groups (P = 0.23). The stroke type and the difference in the levels of urinary Na^+, serum osmolality and urine osmolality were statistically significant between each groups (Table 1).

Table 1

The comparison of the aetiologies of hyponatremia and the demographic, clinical, imaging and laboratory parameters.

Hyponatremic Patients (n-47)	CSWS (n- 24)	SIADH (n-17)	Other (n-6)	P value
Age				
40-59	4(8.51%)	1(2.13%)	0	0.48
60-79	15 (36.17%)	11(23.4%)	6(12.7%)	
>80	5 (10.64%)	5(10.64%)	0	
Gender				0.78
Male	14(29.79%)	8(17.02%)	3(6.38%)	
Female	10(21.28%)	9(19.15%)	3(6.38%)	
Stroke type				
Ischaemic	18 (38.3%)	16 (34.04%)	2(4.26%)	**0.01**
Haemorrhagic	6 (12.77%)	1(2.13%)	4(8.51%)	
Side of the stroke				
Left	13 (27.66%)	3(6.38%)	2(4.26%)	0.12
Right	5 (10.64%)	9(19.15%)	2(4.26%)	
B/L	6 (12.77%)	5(10.64%)	2(4.26%)	
On admission Glasgow coma scale (GCS)	12.58 (SD ± 2.6)	12.82 (SD ± 3.06)	13.83 (SD ± 2.04)	0.56
Systolic blood pressure(mmHg)	151.83 (SD ± 31.37)	151.29 (SD ± 32.14)	166.17 (SD ± 36.27)	0.67
Diastolic blood pressure(mmHg)	87.6 (SD ± 21.46)	89.3 (SD ± 17.8)	90.5 (SD ± 15.9)	0.77
Laboratory investigations				
Serum Na^+ (mmol/l)	130.6 (SD ± 3.05)	129.36 (SD ± 3.9)	130.13 (SD ± 4)	0.58
Urinary Na^+ (mmol/l)	108.6 (SD ± 42.9)	38.6 (SD ± 15.45)	20.4 (SD ± 11.34)	**0.0001**

Serum Osmolality (mosm/Kg)	278.5	276.3	298	**0.04**
Urine Osmolality	(SD ± 14.25)	(SD ± 12.94)	(SD ± 18.5)	
(mosm/Kg)	534.88	349	239.3	**0.0007**
	(SD ± 227.8)	(SD ± 82.5)	(SD ± 74.1)	

[1]Kruskal-Wallis test and Fisher's exact test or Pearson chi square test were performed to get the P value

[2]Bold indicates statistical significance

3.3 Predictors of CSWS in stroke patients

The multivariate logistic regression analysis of CSWS patients revealed that the overall model was not significant {P=0.12, pseudo R^2 = 0.25 with a log likelihood of -24.36 (Table 2)}.

Table 2
Multivariate logistic regression model for CSWS patients (n-47)

	Odds Ratio	**95% confidence interval**		**P value**
Age	0.97	0.88	1.05	0.46
Gender Female	0.32	0.04	2.13	0.24
Hypertension	0.41	0.05	2.89	0.37
Dyslipidaemia	4.4	0.41	47.8	0.22
Diabetes mellitus	5.14	0.81	32.42	0.08
Systolic Blood pressure	1	0.97	1.04	0.71
Diastolic blood pressure	0.95	0.9	1.02	0.19
On admission GCS	0.81	0.56	1.17	0.27
Stroke type Haeamorrhagic	1.54	0.21	11.19	0.66
Side of the stroke Right	0.15	0.02	1.1	0.06

In this group of patients, none of the factors that were considered in the model could predict the occurrence of CSWS in stroke patients.

4. Discussion

Of the 246 stroke patients, 47 developed hyponatremia. Majority of patients developed CSWS. SIADH group comprised of 17 patients and 6 patients had other undetermined causes. There was a significant statistical difference between the aetiologies of hyponatremia and laboratory investigations like urinary Na^+, urinary osmolality and serum osmolality. Demographic characteristics, comorbidities, imaging and clinical parameters like blood pressure, on admission GCS were considered in the multivariate logistic regression model and none of the factors could predict the occurrence of CSWS.

The incidence of hyponatremia in our study group was 19.1%. This finding is consistent with Natarajan et al study which reported incidence of hyponatremia as 20% (13).However there were studies which showed higher hyponatremia incidence as high as 45.3% (15). In our study there was higher incidence of CSWS (51%). In contrast the SIADH group showed lower incidence of 36.2%. These results are in consistent with the study done by Kalita et al where they showed 44.2% of CSWS cases and 7% of SIADH cases. Further they concluded that cerebral salt wasting syndrome as the most common aetiology of hyponatremia in stroke patients (16). However, there were studies which oppose these findings. One such study revealed that out of all the cases of hyponatremia, SIADH was found in 67% of patients and CSWS in 33% of patients (17). There was another interesting study done on hyponatremia in subarachnoid haemorrhage patients in which they have found no cases of CSWS (18).

There was a statistically significant difference in urinary Na^+ levels, S.osmolality and U. osmolality between the aetiologies of hyponatremia. One previous study has shown a significant difference ($P = 0.001$) in urinary Na^+ between SIADH and CSWS (19). However, most of the literature suggests that these parameters could not differentiate the aetiologies of hyponatremia and proper evaluation of the extracellular volume is mandatory (14).

According to our study, the demographic characteristics like age and gender, the comorbidities like hypertension, dyslipidemia and diabetes mellitus, the clinical parameters like systolic blood pressure, diastolic blood pressure and on admission GCS and the imaging data like type of stroke, side of the stroke could not predict the occurrence of CSWS. However, studies have been done to identify the possible predictors of CSWS following SAH previously. One such study has evaluated the importance of using haptoglobin gene as a genetic marker in predicting the CSWS. Haptoglobin gene is associated with the inflammation following SAH and some experts believe that CSWS occurs as a result of this inflammatory process. However the inflammatory process is different among the various groups of haptoglobin genotypes and it was concluded that HP2-2 genotype is an independent predictor of CSWS (12). In contrast, the aneurysm location and the spread of bleeding in SAH do not predict the development of CSWS (11, 20).

5. Conclusion

The incidence of CSWS is higher than the incidence of SIADH. The differentiation of these two entities is important as they have different management approaches. Therefore it is better to have factors which could predict the occurrence of CSWS. However according to our study demographic characteristics,

comorbidities, imaging and clinical parameters like blood pressure, on admission GCS could not predict the occurrence of CSWS.

Abbreviations

CSWS – Cerebral Salt Wasting Syndrome

SIADH- Syndrome of Inappropriate Anti diuretic Hormone secretion

GCS- Glasgow Coma Scale

CI- Confidence Interval

Declarations

1) Ethics approval and consent to participate

Ethical clearance to this study was obtained from the Ethics Review Committee, Faculty of Medicine, University of Peradeniya, Sri Lanka (2018/EC/44).

All methods were performed in accordance with the relevant guidelines and regulations.

Informed consent was obtained from the patient or, in the instance where the patient was not clinically fit to do so or who were dead, from the next of kin and legal guardians.

2) Consent for publication

Not applicable

3) Availability of data and materials

All data generated or analysed during this study are included in this published article.

4) Competing interests (financial and non-financial)

The authors have declared no competing interests exist

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