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MANAGEMENT OF HYPONATRAEMIA IN POST-NEUROSURGICAL PATIENTS

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ABSTRACT

Hyponatraemia (serum sodium <135 mmol/L) is the commonest electrolyte derangement post-neurosurgery. It is associated with higher morbidity, prolonged hospital stay, and highermortality. There is also a significant associated economic burden.Syndrome of Inappropriate Anti-diuretic hormone secretion (SIADH) and Cerebral Salt Wasting (CSW) are the main causes of hyponatraemia in the neurosurgical setting. However, adrenal insufficiency, hypothyroidism, medication side effects, and excessive hypotonic intravenous fluid infusion are also all recognised causes of hyponatraemia. Identifying causes of hyponatraemia and clinical differentiation between SIADH and CSW are vital, as they require different management strategies; fluid restriction for the former versus fluids and salts replacement for the latter. This is an observational prospective study that aims to identify the prevalence and the causes of hyponatraemia in post-neurosurgical patients at Macquarie University Hospital, and in particular to differentiate between SIADH and CSW, and document management used. This study was conducted at Macquarie University Hospital from June 2016 to April 2017. Patients were recruited from ICU and the neurosurgical Ward. Inclusion criteria include any patient with serum sodium <135 mmol/L following pituitary, cerebral or spinal surgery. Patients with prior hyponatraemia, fluid overloadstatessuch as heart failure, liver cirrhosis, and patients on medications that can cause hyponatraemia, for example, thiazides, carbamazepine, haloperidol, and furosemidewere excluded from this study.Statistical analysis was performed using SPSS Version 24; student t-test was used with a P value <0.05 considered as significant. Total 38 patients in total were recruited. The prevalence of hyponatraemia in post-neurosurgical intervention was 6.1%. Most of the patients were asymptomatic. We classified the hyponatraemic patients according to aetiology into five groups: 16 patients with SIADH (42.1%), 15 unclassified patients (39.5%), 3 patients with CSW (7.9%), 3 patients with adrenal insufficiency (7.9%), and one patient with hypothyroidism (2.6%). Despite the fact that both clinical and biochemical parameters of SIADH and CSW were quite similar, we could differentiate between the two conditions depending on the state of dehydration (P-value<0.01). Hyponataremia is common following neurosurgery. It is often multifactorial, and it is essential to identify the aetiology of hyponatraemia in each individual patient in order to address the appropriate treatment. SIADH is the commonest cause of hyponatraemia, followed by unclassified cases, CSW, adrenal insufficiency, and hypothyroidism. Fluid restriction is the most common treatment modality for treating hyponatraemia, yet it can not be used in all cases. It can cause deleterious consequences in patients with CSW, and adrenal insufficiency as patients in these categories are volume depleted.

Keywords: hyponatraemia, SIADH, CSW, and neurosurgery

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INTRODUCTION

Hyponatraemia is the commonest electrolyte derangement post- neurosurgery, with an estimated incidence of 0.81-15%. In most cases, it is attributed to one of two distinct syndromes: Syndrome of Inappropriate Anti-Diuretic Hormone secretion (SIADH) or Cerebral Salt Wasting Syndrome (CSW)[(1)]. Hyponatraemia may also be caused by disorders such as adrenal insufficiency, hypothyroidism, vasopressin therapy for diabetes insipidus (DI), excessive fluid intake and other fluid overloaded states such as cardiac, renal or hepatic failure [(2-4)]. The degree of hyponatraemia varies from mild to severe, and it is highly affected by type and extent of pathology, and the nature of the neurosurgical intervention. Hyponatraemia is associated with significant morbidity and can result in mortality due to cerebral oedema [(1)].

Epidemiology

Hyponatraemia (defined as serum sodium of < 135 mmol/L) is the commonest electrolyte derangement post- neurosurgery. It can complicate a number of neurosurgical conditions, such as traumatic brain injury (TBI; 20% of them develop hyponatraemia), subarachnoid hemorrhage (SAH; 40-50% are complicated by hyponatraemia), intracerebral and pituitary tumors, and spinal pathologies[(2)]. Hyponatraemia and/or its inadequate treatment have major impacts on neurosurgical patients, including cerebral vasospasm, seizures, cerebral oedema, and death. Moreover, management of hyponatraemia costs more than 3.5 billion dollars in The United States of America annually[(3)]. Hyponatraemia can be caused by endocrine disorders such as adrenal insufficiency, hypothyroidism, over treatment of Diabetes insipidus (DI) with vasopressin, and excessive intake of hypotonic fluid[(4)]. Hyponatraemia is associated with increased morbidity, higher hospital stay, and increased mortality in the most severe forms (mortality rate is 25% in severe hyponatraemia < 120mmol/L, and 9.3% if serum sodium > 120mmol/L)[(1,5)].

Hyponatraemia is the commonest electrolyte disturbance in hospitalised patients following neurosurgery, with an approximate incidence of 0.81-15%. Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH), and Cerebral Salt Wasting (CSW) have been implicated as major aetiologies for hyponatraemia[(1,2)]. Studies have been conducted to differentiate between SIADH and CSW as these two conditions are overlapping and their management is the opposite; fluid restriction in the former versus fluid replacement in the latter. Most studies could not differentiate between these two conditions solely on biochemical parameters. Rather volume and hydration status were more useful for differentiating between these two disorders[(2-10)]. Other endocrine disorders such as adrenal insufficiency and hypothyroidism are not uncommon causes of hyponatraemia[(4)]. Proper management of hyponatraemia is essential to reverse its adverse consequences[(20)].The following databases have been searched for the period from June 2016 until April 2017: PubMed, using MeSH terms 'Hyponatraemia', and 'Neurosurgery', Ovid Medline, EMBASE,

and Scopus using MeSH terms and keywords 'Hyponatraemia', and 'Neurosurgery', 'SIADH'. Furthermore, Google Scholar hand searching method has been used. All types of study were included; reviews, retrospective studies, case reports, commentaries, guidelines, controlled trials and systematic review.

Pathophysiology of hyponatraemia post-neurosurgery due to SIADH

SIADH was first described by Schwartz and coworkers in 1957[6]. It usually happens when neurosurgical manipulation, bleeding, stress, pain, and nausea cause an increment in the secretion of ADH (a peptide hormone secreted by the posterior pituitary gland). Excessive ADH production can also be caused by medications, such as anticonvulsants; carbamazepine and lamotrigine (all excluded in this study). ADH acts mainly on the renal distal convoluted tubule (DCT) by enhancing free fluid reabsorption through aquaporin-2(AQP2) insertion in kidney tubules leading to intravascular volume expansion. The latter leads, with thirst stimulation induced by ADH, into a state of hypo-osmolar (dilutional) hyponatraemia. Furthermore, the resultant intravascular fluid expansion leads to natriuresis by two separate mechanisms: firstly, it causes an increase in glomerular filtration rate (GFR) leading to decreased sodium reabsorption in the renal proximal convoluted tubule (PCT); secondly, it causes inhibition of the renin/ aldosterone axis which leads to further reduction in sodium reabsorption[7]. SIADH can be a part of triple phase response after neurosurgical procedures, in which hypothalamus-pituitary manipulation leads to disruption of ADH secretion resulting into diabetes insipidus (DI), which lasts for 4-8 days. Following that, a transient remission interval characterized by an excessive secretion of ADH lasts for 1-14 days and ends eventually into a state of permanent DI[8]. SIADH can be diagnosed clinically in any hyponatraemic patient with the following biochemical criteria: low serum osmolality < 275 mosmol/L, high urine osmolality >100 mosmol/kg with urine to plasma osmolality ratio >1, high urinary sodium > 20-30 mmol/l, with normal underlying renal, hepatic, adrenal and thyroid functions. A low hematocrit (PCV), serum urea, and serum uric acid are additional supportive features to diagnose SIADH[2-8].

Pathophysiology of hyponatraemia post-neurosurgery due to CSW

CSW, or sometimes referred as RSW (renal salt wasting), was first described by Peters et al in 1950 in the background of severe hyponatraemia and cerebral vasospasm in a patient with subarachnoid hemorrhage (SAH). The aetiology of hyponatraemia in CSW was not fully understood at that time[6]. Subsequently, it was postulated that CSW is characterized by excessive natriuresis due to decrease neuronal input to the kidneys in patients with a neurosurgical insult. This drop in sympathetic drive leads to the release of natriuretic peptides (Atrial natriuretic peptide, Brain natriuretic peptide, C-natriuretic peptide, and Oubain or D natriuretic peptide). These peptides enhance volume and sodium loss via the kidneys and also inhibit renin production despite the presence of hypovolaemia[9]. The main biochemical features that occur in patients with hyponatraemia due to CSW are low serum osmolality < 275 mosmol/l, high urine osmolality > 100 mosmol/kg, and a urine/ plasma osmolality ratio >1, and high urine sodium >30 mosmol/l. All these biochemical features are quite similar to those in SIADH. However, CSW can have distinct biochemical features, although not essential to the diagnosis, include high hematocrit, and high serum urea and serum uric acid[9,10]. In 2005, Revilla-Pacheco conducted a retrospective study on patients with aneurysmal SAH and concluded that most cases of hyponatraemia complicating aneurysmal SAH were due to CSW[11]. CSW can

coexist with diabetes insipidus (DI), as both conditions are associated with natriuresis which may add a layer of complexity to the diagnosis [12].

Pathophysiology of hyponatraemia post-neurosurgery due to Adrenal insufficiency: Corticosteroid insufficiency is a not uncommon cause of hyponatraemia in post-neurosurgical patients[2]. Any neurosurgical manipulation, cerebral bleeding, or pituitary gland surgery can cause interruption to ACTH secretion. Low ACTH stimulates ADH secretion by two mechanisms. Firstly, it stimulates corticotrophin secreting hormone (CRH) secretion by the hypothalamus via positive feedback. This is almost always accompanied by an increment in ADH secretion; such effects are mediated by rapid, direct vasodilation induced by CRH that decreases baroreceptor input to the brain stem, leading to a rapid release of AVP that induces the antidiuresis by direct action on the V_2Rs in the kidney. Simultaneously, acting on V_2Rs in the heart, AVP inhibits ANP release and synthesis, resulting in a decrease in renal cGMP output that is responsible for the antinatriuretic and antikaliuretic effects. Secondly, a significant fall in ACTH level may lead to cortisol deficiency, leading to multiple effects including reduced vascular tone and reduced sodium absorption, which can cause a fall in blood pressure. This stimulates ADH release to counteract hypovolaemia[13]. Hence patients with hyponatraemia due to ACTH/ cortisol deficiency may have similar biochemical characteristics to SIADH patients e.g. serum osmolality < 275 mosmol/L, urine osmolality > 100 mosmol/kg and urine to plasma osmolality ratio > 1, urinary sodium > 20-30 mmol/l, plus normal underlying renal, hepatic, cardiac and thyroid function. Such case may be identified by low ACTH (< 15 mcg/dL or 414 mmol/L), and low baseline serum cortisol (< 10 mcg/dL or 284 mmol/L), or serum cortisol level < 18 mcg/dL (< 497 mmol/L) at 30-60 min after 250 mcg ACTH stimulation test[2,4,13,14].

Pathophysiology of hyponatraemia post-neurosurgery due to hypothyroidism

Any cause of hypothyroidism (whether primary, secondary or tertiary) may be associated with hyponatraemia. For each 10 mIU/L rise in thyroid stimulating hormone (TSH)) level, serum sodium falls by 0.14 mmol/L. It has been postulated that patients with hypothyroidism have reduced cardiac stroke volume, leading to loss of ADH suppression due to carotid baroreceptors stimulation. Hypothyroidism is also associated with lower renal GFR and reduced free water excretion in the DCT, which may lead to fluid overload state and dilutional hyponatraemia[4].

SIADH Vs CSW

Differentiating SIADH from CSW is of great importance as their treatments are quite different; fluid restriction in the former versus fluid and salt replacement in the latter. Differentiation is often difficult due to clinical and biochemical overlap between these two syndromes[10]. Neither the degree of hyponatraemia nor the level of ADH helps differentiate between SIADH and CSW as most patients with CSW are volume deplete and this leads to increased levels of ADH as a positive feedback mechanism to counteract the volume depletion[9]. A fractional excretion of urate (FEUr %), which is the{ serum creatinine*urine urate/serum urate*urine creatinine)*100} with a normal value of 4-11%, represents the solute (urate) excretion by the kidneys, and has been proposed by some experts to help differentiate between SIADH and CSW, as sodium correction by fluid restriction helps to restore FEUr % to normal in SIADH, but not in CSW[16]. Similarly,

Imbriano and colleagues 2016 proposed that serum urate and FEUr % were sufficient as differentiating points between SIADH and CSW during follow-up of four paediatric patients with hyponatraemia[17]. In contrast, other authors eg, (Maesaka 2014) did not find FEUr % helpful in differentiating between the two[10]. Hematocrit, serum creatinine, and serum urate are sometimes higher in CSW, however, these are not pathognomic features. Some cases of CSW may have an unexplained low serum uric acid[8]. Hence the only reliable differentiating feature between the two conditions is the extracellular volume status (ECV); hypovolaemia with a negative fluid and salt status are pathognomic of CSW and help to differentiate it from SIADH[9]. Hypovolaemia can manifest itself clinically as hypotension, tachycardia, lack of sweating, decreased skin turgor, sunken eyes, and dry mucous membranes[5]. Low central venous pressure (CVP) < 6 mm Hg and/or low pulmonary capillary wedge pressure < 8 mm Hg are very useful parameters to diagnose patients with hypovolaemia in the intensive care unit[8,10]. Other measures that have been used to detect hypovolaemia in hyponatraemic patients include daily weighs, radioisotope dilution techniques (labeled red blood cell studies), and echocardiography[10]. However, these are either not widely validated or difficult to implement. Furosemide test has been mentioned in some of the literature as a differentiating test by using 20 mg infusion of furosemide which helps to bring serum sodium to normal in SIADH but not in CSW patients[2].

Treatment of hyponatraemia

Whenever there is an obvious reversible cause of hyponatraemia, it should be treated. It has been reported that unsteady gait, falls, osteoporosis and fractures are increased by up to four folds for levels of sodium in the range of 115-132 mmol/L[20]. In acute and/ or severe hyponatraemia, serum sodium level should be corrected urgently to prevent deleterious neurological consequences including seizures, obtundation, or brainstem herniation due to cerebral oedema and raised intracranial pressure. These consequences can be prevented and raised intracranial pressure decreased by 50% by moderate elevation of serum sodium by 4-6 mmol/L in the first four hours[1]. This can be achieved by infusing a bolus of 100 ml hypertonic saline (3% NaCl) over 10-15 minutes and can be repeated 2-3 times a day for a target not exceeding 12 mmol/L over 24 hours, and an additional 8 mmol/L during every 24 hours until the patient's sodium level reaches 130 mmol/L[2]. In less severe cases, a target sodium correction of 6-8 mmol/L over 24 hours with a correction rate of 0.5-2 mmol/kg is recommended. This should be given under a physician's monitoring with frequent sodium measurement as rapid and unsupervised correction of hyponatraemia can result in pontine demyelination[1,2]. In SIADH**,**many treatment modalities have been used including: Fluid restriction(FR), which remains the primary method of treatment of euvolaemic SIADH. Drawbacks include a relatively slow rate of sodium correction, risk of enhancing cerebral vasospasm in volume-depleted patients, issues with compliance and monitoring in some patients plus risk of overtreatment and dehydration [21]. Amount of FR depends on sodium levels; for a serum sodium of 130-134 mmol/L, recommended FR is 1200 ml/day; for serum sodium of 126-130 mmol/L, recommended FR is 800 ml/day; for severe hyponatraemia (serum sodium of <125), recommended FR is 600 ml/day[22].Demeclocycline, oral furosemide, and salts tabletshave been used for mild to moderate hyponatraemia in the outpatient setting, but with no strong evidence of their benefit[2,3,8]. Demeclocycline is no longer available in Australia. Urea is an osmotic diuretic to enhance excessive water loss, and decrease sodium loss. It was introduced as an intravenous preparation in

1985. Drawback includes the bitter taste of oral preparations; hence an intravenous solution of 40 mg urea dissolved in 100-150 ml normal saline given by 8 hourly drips for 1-2 days at 60-100 ml/hour has been developed. Urea as a therapy is contraindicated in patients with significant renal, heart or hepatic impairment or failure, and in volume-depleted patients[23]. In recent times an oral preparation of urea 10 grams + sucrose 200 mg + citric acid 1.5 gm + NaHCO3 2 gm has been used as an alternative to nonpalatable urea powder. Oral urea is administered at a rate of 0.25-0.5 g/kg/day[19]. However, there is limited data on its actual efficacy[2]. Finally,Vaptans:or vasopressin 2 receptor antagonists. These medications were first described in 1992; they act as competing blockers to the action of ADH (also known as arginine vasopressin or AVP) on V2 receptors in the adrenal medulla, thus inhibiting water reabsorption. They are helpful in increasing free water excretion, raising sodium levels, minimising the risk of cerebral oedema, and reducing the length of hospital stay. Conivaptan and Tolvaptan are members of this class of medications, approved by the FDA in 2005 and 2007 respectively for treatment of hyponatraemia in SIADH patients[24]. They are TGA approved in Australia but not available on the PBS. Andrea Kleindienst described that these medications are relatively safe and free from side effects, apart from a minimal elevation in liver enzymes, and there were no reported cases of pontine demyelination syndrome [25]. Conivaptan is also available as an intravenous preparation that can be used in SIADH patients outside the ICU setting, as it approved its effectiveness and safety[26]. In CSW, water and salts should be replaced in patients with hyponatraemia due to CSW[9]. 12 grams of NaCl + 50ml/kg normal saline are sufficient to correct serum sodium over 24-48 hours[10]. Fludrocortisone in a dose of 0.1-0.4 mg/day can also be used[9,10]. In adrenal insufficiency and hypothyroidism:hyponatraemia in these entities can be reversed by giving hydrocortisone and thyroxine respectively. Caution should be exercised using FR and glucocorticoids replacement in known adrenal insufficiency as it can lead to rapid uncontrolled rise in sodium and risk of pontine myelinolysis[4,9,14].

MATERIAL AND METHODS

Patients were included if their serum sodium was < 135mmol/L, and if they had cerebral, pituitary, or spinal surgery.Patients with prior hyponatraemia, congestive heart failure, liver cirrhosis, and those on medications that can cause hyponatremia, such as diuretics (eg.frusemide), anticonvulsants (eg. carbamazepine), psychotropics (eg. haloperidol), and thiazides were excluded from this study.A thorough physical examination was done including assessment of the state of hydration, input and output chart, BP, and CVP.Each patient has been assessed for 1. BUN, serum creatinine and serum electrolytes using the ISE module of the COBAS INTEGRA systems which are intended for use in the quantitative determination of sodium, potassium, and chloride in diluted serum and plasma using ion-selective electrodes.2. Serum uric acid using Roche enzymatic colorimetric test. 3. Serum osmolality using osmometer operation procedure. 4. Serum ACTH, cortisol, TSH and free T4 using CMIA (Chemiluminescent Microparticle Immunoassay). Spot urine sodium, creatinine, urate, and osmolality by The ISE module of the COBAS INTEGRA and osmometer operation procedure respectively.All tests were performed by Douglas Hanly Moir (DHM) Pathology at Macquarie University Hospital.A fractional excretion of urate (FEUr %) was calculated for each patient using the formula (serum creatinine*urine urate/serum urate*urine creatinine)*100, by using a software formula. All the information was kept in the patients' records on the Trakcare system at Macquarie University Hospital. The investigators alone could access this information. All patients were de-identified

using numbering coding system.This is a prospective observational study. Student t test with significant P Values of 0.05 and CI of 95 % have been used.This study was submitted to Macquarie University Ethics Committee on 09/05/2016. A further amendment to the protocol was made on 15/05/2016. The research met the requirement set out in the National Statement on Ethical Conduction in Human Research (2007 updated in May 2015). It was approved on 22/06/2016 reference number 5201600362. Informed written consent was obtained from 36 patients and witnessed verbal consent was obtained from 2 patients. The purpose of the study, tests involved, possible costs (minimal), and follow-up were explained to all patients. No grant or funding was submitted. Pathology tests performed through Douglas Hanly Moir Pathology. As the research was conducted with current Australian best practice guidelines, costs were covered by Medicare and/or through patients' private health funds.

RESULTS

The prevalence of hyponatraemia in post-neurosurgical patients at Macquarie University Hospital was estimated to be 6.1%.

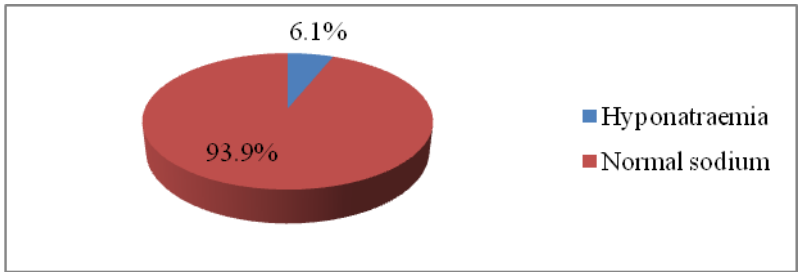

Figure1: Prevalence of hyponatraemia

Most of the patients with hyponatraemiawere asymptomatic as in figure 2.

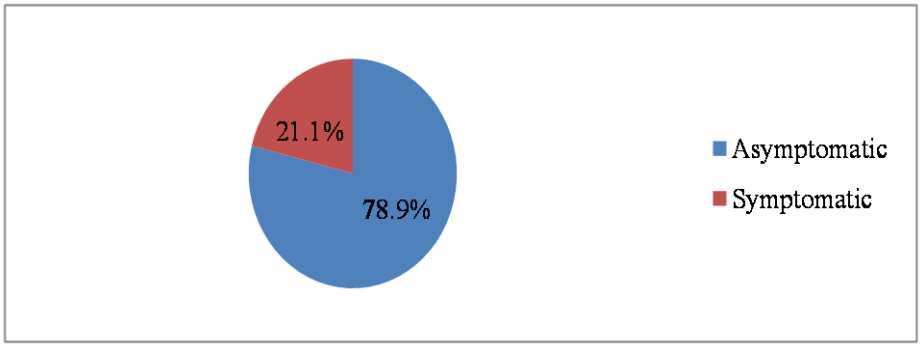

Figure 2: Symptoms associated with hyponatraemia

The patients with hyponatraemia were classified according to aetiology into 5 groups: 16 patients with SIADH (42.1%), 15 unclassified patients (39.5%), 3 patients with CSW (7.9%), 3 patients with adrenal insufficiency (7.9%), and one patient with hypothyroidism (2.6%) as shown in Figure 6. The unclassified group includes patients whose low serum sodium could not be fitted into a specific category (unclassified group), either because these were discharged early before they completed the investigations, or because they declined some of the tests. The unclassified category also includes patients with over treatment of diabetes insipidus with vasopressin and excessive hypotonic fluids. Aetiological classifications according to the type of neurosurgical interventions are shown in figure 3

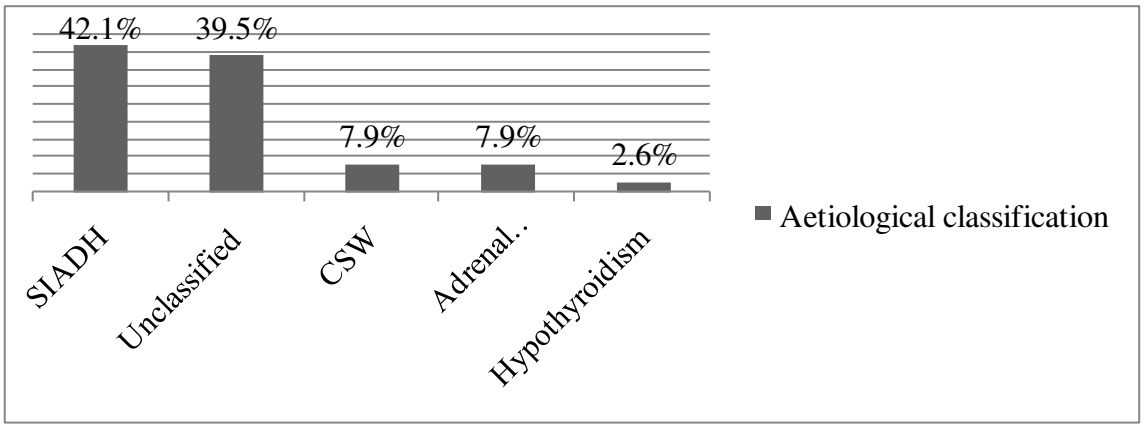

Figure 3: Aetiological classification of hyponatraemia in general

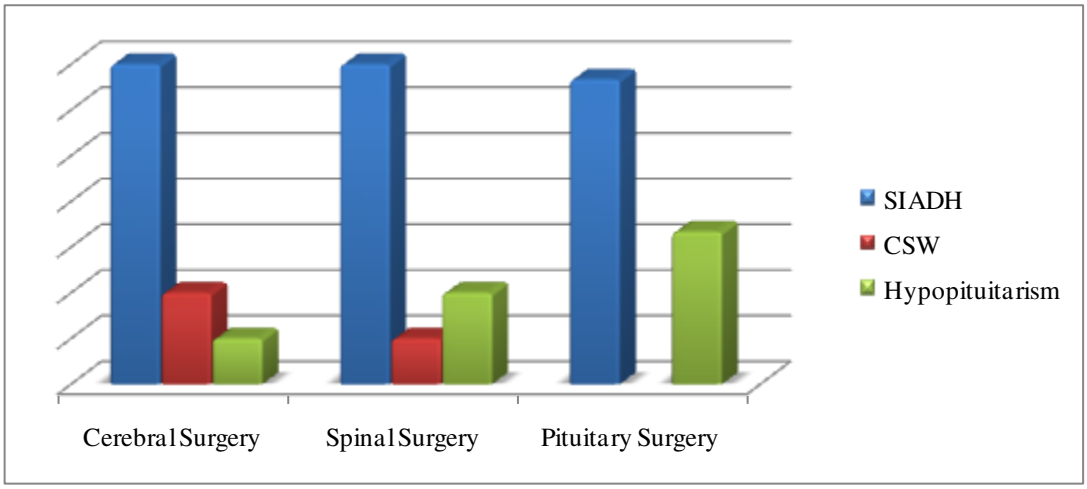

Figure 4: Aetiological classification according to the type of neurosurgical intervention.

SIADH Vs CSW

The biochemical parameters between SIADH and CSW groups have shown no significant differences between them, apart from urine osmolality which was slightly higher in patients with CSW than in patients with SIADH, with a P-Value of 0.047 as shown in Table 2.

Table 1: Biochemical difference between SIADH and CSW

Parameters	SIADH	CSW	P value
S.Na	129.8 ± 3.8	129.6 ± 2.0	0.9
S. Osmolality	284.0 ± 8.9	285.3 ± 4.1	0.8
Cortisol	301.3 ± 179.7	281.6 ± 224.5	0.8
S. uric acid	0.3 ± 0.1	0.1 ± 0 .04	0.3
S.Cr	90.9 ± 30.9	68.3 ± 24.7	0.6
GFR	65.5 ± 18.7	71.0 ± 16.8	0.5
U.Na	4.9 ± 2.6	6.0 ± 4.4	0.5
U. Osmolality	454.0 ± 156.4	689.3 ± 359.8	**0.047**
U.Cr	3.6 ± 2.4	1.3 ± 5.7	0.2
U.Uric acid	1.2 ± 1.4	0.3 ± 0.5	0.1
FR%	1.7 ± 3.6	2.3 ± 3.6	0.6

According to patients' state of hydration (skin turgor, pulse rate, and tongue moisture), all patients in SIADH group were euvolemic in comparison to only one patient in CSW group, while 2 patients in CSW group were hypovolaemic in comparison to nil in SIADH group as in table 2.

Table 2: Clinical differences between SIADH and CSW groups

Fluid status	CSW	SIADH	P value
Euovolaemic	1 (33.3%)	16 (100%)	**<0.01****
Hypovolaemic	2 (66.7%)	0 (0.0%)	
Total	3	16	

Neither the mean blood pressure (MBP) nor the central venous pressure (CVP) was significantly different between patients in the SIADH and CSW groups as shown in Tables 3 and 4 respectively. However, there was a nonsignificant trend towards CSW patients having lower mean blood pressure, reflecting the lower volume status of CSW patients compared to SIADH patients.

Table 3: MBP differences between SIADH and CSW groups

Mean blood pressure		
Groups	**Means ± SD**	**P Value**
SIADH	85.3 ± 6.7	0.06

CSW	75.6 ± 12.5	

Table 4: CVP differences between SIADH and CSW groups

Classification	CVP	
	Means ± SD	**P value**
SIADH	8.3 ± 1.7	0.3
CSW	7.3 ± 1.1	

Treatment modalities of hyponatraemia in different groups are illustrated in Table 5.

Table 5: Treatment modalities in different groups with percentages of treated patients

Treatment Modality	SIADH	CSW	Adrenal insufficiency	Hypothyroidism	Unclassified
None	18.8	0.0	0.0	0.0	93.3
Fluid restriction (FR)	43.8	33.3	0.0	0.0	0.0
Salt tablets	31.3	0.0	0.0	0.0	0.0
Hypertonic saline (3%	37.5	33.3	0.0	0.0	0.0
Thyroxin	0.0	0.0	0.0	100.0	0.0
Hydrocortisone	0.0	0.0	100.0	0.0	0.0
Normal (0.9% saline)	0.0	33.3	0.0	0.0	6.7
Urea	6.3	0.0	0.0	0.0	0.0
Fludrocortisone	0.0	33.3	0.0	0.0	0.0

DISCUSSION

Hyponatraemia following neurosurgical intervention is the most frequent, yet challenging electrolyte abnormality that occurs, due to the fact that hyponatraemia is often multifactorial[27,28]. In recent years, identifying causes of hyponatraemia and, in particular, differentiating between SIADH and CSW have been matters of significant debate[10]. In this study, we highlight the important steps in the management of hyponatraemia in the post-neurosurgical patient. We recruited 38 eligible patients (out of a total 602 patients undergoing different neurosurgical procedures at Macquarie University Hospital over the period of 10 months from June 2016 to April 2017). The prevalence of hyponatraemia post-neurosurgical intervention at Macquarie University Hospital was 6.1% as shown in figure (1), and this prevalence goes with what mentioned in most of the literature[1,2,3].As shown in figure (2), only 21% of patients with hyponatraemia were symptomatic, while the majority had no symptoms; this corresponds to literature reports[29]. We classified the patients according to their clinical status and their biochemical parameters (figure 3) into five

groups: SIADH, CSW, adrenal insufficiency, hypothyroidism, and unclassified groups. The last group includes patients whose their low serum sodium could not be fitted into a specific category, either because they were discharged early before completing the investigations, or because they declined some of the tests. The unclassified category also included patients with overtreatment of diabetes insipidus with vasopressin or excessive hypotonic fluids. Our study show SIADH as the most common cause of hyponatraemia among all post-neurosurgical patients with a prevalence of 42.1% (16 patients) followed by unclassified 39.5% (15 patients), CSW 7.9% (3 patients), adrenal insufficiency 7.9 % (3 patients), and only one patient (2.6%) with hypothyroidism (Figure 4). Further aetiological classification of hyponatraemia, according to the sub-type of neurosurgical intervention (cerebral versus spinal versus pituitary) has been illustrated in figure (5). Amonsgt patients undergoing cerebral surgery SIADH is the predominant cause (70% prevalence), followed by CSW (20%), and finally hypopituitarism (adrenal insufficiency and hypothyroidism) with 10% prevalence. In patients undergoing spinal surgery, SIADH is again the most common, followed by hypopituitarism and then CSW. While in the two pituitary adenoma surgery patients, there were no cases of CSW (SIADH was first followed by hypopituitarism); this finding is similar to the case report by Gurreno 2007; CSW usually does not complicate pituitary tumor surgery[7]. Our study had only one case of SAH; her low serum sodium was attributed to SIADH rather that CSW. This finding is disconcordant with most of the literature which reports CSW to be the most common cause of hyponatraemia in patients with SAH[9,10]. Nevertheless, Hannon and his colleagues have mentioned in a published prospective study in 2013 that most hyponatraemia cases following aneurysmal SAH are due to SIADH, and adrenal insufficiency rather than CSW, depending on the clinical and biochemical parameters[30]. The biochemical profiles in patients with SIADH and CSW were quite similar, apart from the urine osmolality which was slightly higher in CSW patients (Table 1). Most of the literature could not differentiate between the two conditions depending solely on the biochemical parameters[2,10]. Clinically, we could not differentiate between SIADH and CSW patients using their mean blood pressure (MBP) (P = 0.06, with a trend to significance), or central venous pressure (CVP) (P =0.3) as shown in Tables 2, and 3 respectively. This can be attributed to two main reasons: Firstly, our overall patients' cohort was small and this can adversely impact demonstration of statistical significance. Secondly, accurate assessment of volume status ideally performed using more sophisticated measures of total blood volume such as the use of Chromium labeled autologous erythrocyte, or radio-iodinated albumin. Such tests were not available to our study due to prohibitive costs[10]. However, we did attempt to classify patients into euvolaemic or hypovolaemic categories by clinical assessment of their hydration status using tongue moisture, and skin turgor (table 4). This showed a significant difference in volume status; all SIADH appeared to be euvolaemic in comparison to only one patient with CSW, while two patients with CSW were hypovolaemic in comparison to nil patient in the SIADH category (P Value < 0.01). Treatment modalities of patients with hyponatraemia are shown in the table (5) and reveal that patients with SIADH were treated mostly by fluid restriction (FR) at 800-1200 ml/day, followed by salts tablets (NaCl) 9-12 grams/day, and only one patient received urea sachets. Six patients with SIADH had severe hyponatraemia (< 125 mmol/L) and were treated with 3 % saline in the ICU. Some SIADH patients with mild hyponatraemia received no treatment and sodium self-corrected. The three patients with CSW were treated as follows: one patient was fluid restricted and deteriorated neurologically. She became confused and had seizures, and was transferred to the ICU where she received hypertonic saline. She had a subsequent cerebral angiogram which showed

severe cerebral vasospasm for which she received intracerebral verapamil injection. The second patient was treated with hypertonic saline initially as her sodium was markedly reduced (122 mmol/L), and the last patient received 0.9 % saline and 0.04 mg/day fludrocortisone tablets. The three patients with adrenal insufficiency were diagnosed based upon low morning cortisol < 10 mcg/dL. One of them was clinically hypotensive and had a syncopal episode. His blood pressure and serum sodium were restored to normal by the initiation of hydrocortisone replacement. Despite the fact that we did not confirm their adrenal insufficiency by doing insulin tolerance test (ITT) immediately after operations or by ACTH (Cosyntropin) test in three months postoperatively, we managed to correct their hyponatremia by glucocorticoid replacement.

Finally, there was only one patient who she already had hypothyroidism (TSH 11, and T4 4 mcg/dL), and she was on thyroxine 50 mcg/day. Her sodium was normalized when we optimised her thyroxine dose to 100 mcg/day.

This study had the following limitations:

1. Many patients were not recruited in this study, either because of the late notice or due to mild hyponatraemia (130-134 mmol/L), so their treating doctors were not keen to treat such mild hyponatraemia.
2. For patients with suspected adrenal insufficiency, confirmatory tests (insulin tolerance immediately following operations, or ACTH suppression test in three months postoperatively) had to be done, but we did not get to do them.

3. FEUr % should be rechecked after sodium correction as an additional test to differentiate between SIADH and CSW, as FR helps to normalize FEUr % in SIADH but not in CSW. However, a number of patients could not be rechecked due to early discharge.

CONCLUSION

Hyponatraemia is a common electrolyte abnormality in post-neurosurgical patients. It is asymptomatic in the majority of the patients. However, more severe cases can be associated with higher morbidity, adverse neurological sequelae, and increased the length of hospital stay. Hyponatraemia is often multifactorial, and it is essential to identify the aetiology of hyponatraemia in each individual patient in order to institute appropriate treatment. SIADH is the commonest cause of hyponatraemia in the post-neurosurgical setting followed by unclassified cases, CSW, adrenal insufficiency, and hypothyroidism. Fluid restriction is the most common treatment modality but is not appropriate for use in all cases as it can have deleterious consequences if applied in patients with CSW, or adrenal insufficiency, as both these category patients are volume depleted. SIADH is difficult to differentiate from CSW biochemically due to the large overlap between the two conditions. However, in our study, they could be differentiated clinically through careful assessment of patients' volume and hydration status.

For future studies, the patient's sample needs to be increased, and more patient-derived clinical data may be used to differentiate SIADH and CSW including Pulmonary Capillary Wedge Pressure (PCWP), echocardiography, and FEUr% before and after sodium correction. It would be useful to incorporate patients in the neurosurgical setting to other inpatients' settings including serious medical and orthopedic surgery, GI surgery, etc.Monitoring serum sodium, hydration status and volume status are important elements to optimise patients' recovery post neurosurgery and minimise the risk of complications and prolonged hospital stay.

ETHICAL CLEARANCE

The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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