TYPE: BRIEF COMMUNICATIONS

NOTE: *BC's main text should not exceed 1500 words.*

TITLE: *(No more than 35 words.)*

Managing Hyponatraemia secondary to Primary Polydipsia – beware too rapid correction of hyponatraemia

ABSTRACT: *(Provide unstructured abstract of no more than 65 words.)*

We describe three cases of severe hyponatraemia in the setting of primary polydipsia that were managed in our centre in 2016. Despite receiving different solute loads, large volume diuresis and rapid correction of serum sodium occurred in all cases. Given the potentially catastrophic consequence of osmotic demyelination, we highlight the judicious use of desmopressin and hypotonic fluid infusion to mitigate sodium overcorrection in this setting.

KEYWORDS: *(Five key words in order of importance for indexing purposes should be supplied below the abstract and should be taken from those recommended by the US National Library of Medicine's Medical Subject Headings (MeSH) browser list at <http://www.nlm.nih.gov/>)*

Water-Electrolyte Imbalance

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Polydipsia, Primary

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MAIN TEXT: *(Provide case study example and a review of relevant medical literature; e.g. highlight approximately 20 case examples.)*

Introduction

Hyponatraemia is an increasingly common problem in ageing hospitalised populations. It requires meticulous management with close attention to the rapidity of normalisation of the serum sodium level. While the Syndrome of Inappropriate Anti-diuretic Hormone (SIADH) is the most common cause of hyponatraemia, primary polydipsia (PP) is also encountered. Management of hyponatraemia in the setting of PP is similar to the treatment of SIADH despite differing underlying physiological mechanisms. There are unique management issues, however, that occur in PP. Here we report three cases of primary polydipsia, treated at our centre between February and March 2016. These highlight the large volume diuresis which can occur with treatment of hyponatraemia in PP and potentially result in rapid sodium overcorrection with catastrophic consequences.

Case Report

Patient 1

Patient 1 was a 22 year old female travelling from Thailand, who presented with confusion and seizures. She had a past history of anorexia nervosa and had been consuming over 10L of water daily for approximately 2 years. Her presentation was precipitated by acute ingestion of an unquantified amount of water after disembarking from a flight. However, due to her initial altered conscious state, this information was not available until later in the clinical course. At presentation her serum sodium was

112mmol/L and osmolality 234mOsm/kg, with paired urine sodium of less than 20mmol/L and urine osmolality of 79 mOsm/kg . Cortisol and TSH were normal. She was managed with fluid restriction and 20mL of 3% hypertonic saline over one hour and transferred to the intensive care unit. Six hours following the hypertonic saline, she had voided a total of 4750mL and her sodium had risen to 130mmol/L (Figure 1a). She was treated with two intravenous doses of 2µg desmopressin, 3 hours apart to achieve a reduction in urine output, and received intravenous 5% dextrose. Her sodium was re-lowered to 118mmol/L at 23 hours post commencement of treatment. The sodium was re-lowered a second time at 34 hours post treatment with intravenous 5% dextrose boluses alone, after a 2835mL diuresis in one hour and a rapid rise to 131mmol/L. Stabilisation to 135-137mmol/L occurred after 54 hours and she was transferred to the ward where fluid intake was controlled.

Patient 2

Patient 2 was a 60 year old female who presented with collapse, a head laceration, and confusion. She had a past history of anxiety, and had been consuming over 5L of water daily. Prior to presentation she reported an urge to drink water and stood in the shower for approximately 4 hours doing so. Her serum sodium on presentation was 114mmol/L. She initially received 42mL/h of normal saline while she underwent trauma investigation. Ten hours later, her serum sodium was 121mmol/L, osmolality 253 mOsm/kg and urine sodium less than 20mmol/L with osmolality of 62 mOsm/kg . Cortisol and TSH were normal. She was admitted to the intensive care unit and initially managed with fluid restriction. At 12 hours her serum sodium had increased to 135mmol/L and total urine output was 6485mL (Figure 1b). Due to uncertainty about the chronicity of the hyponatraemia, she was treated with 1µg desmopressin intravenously concurrently with 5% dextrose in water to re-lower the serum sodium to 127mmol/L. Her

sodium was allowed to increase to normal range over the next 13 hours, where it remained throughout her admission, maintained on a 3L fluid restriction.

Patient 3

Patient 3 was a 63 year old female who was an inpatient when she developed hyponatraemia. She was admitted under the neuropsychiatric team and had a formal diagnosis of primary polydipsia. Although her treatment plan included a 2L fluid restriction she was reported to be surreptitiously drinking from shower and basin taps. She developed SIADH secondary to aspiration pneumonia, with a sodium of 113mmol/L discovered during investigation for haemodynamic instability and agitation. Paired serum osmolality was 237mosm/kg; urine sodium was 68mmol/L and urine osmolality was 365 mOsm/kg. Her serum sodium was 137mmol/L four days prior to this deterioration. She was transferred to intensive care and received 250mL of 3% hypertonic saline over 2 hours. Her sodium increased by 19mmol/L over 24 hours associated with a diuresis of 4730mL (Figure 1c). It was stabilised with a 1.2L fluid restriction over the next 48 hours. She continues under close follow-up by the neuropsychiatry team.

Discussion

Primary polydipsia has been reported in up to 20% of psychiatric patients, and is particularly associated with schizoaffective disorders, eating disorders, anxiety and bipolar affective disorders.¹⁻² The

pathophysiological mechanisms are likely to be multifactorial including resetting of the osmostat and malfunction of hypothalamic thirst centres.¹

When water intake exceeds the excretion capacity of the kidney with acute high volume hypotonic fluid ingestion, as in our first two cases, hyponatraemia ensues.¹ Additionally, patients with PP have been found to be more sensitive to anti-diuretic hormone (ADH) at the level of the renal tubule collecting duct.³ Thus, any condition that promotes ADH secretion, including nausea, pain, psychosis, or SIADH can result in rapid and profound hyponatraemia.

The European Society of Endocrinology (ESE) and a United States expert panel (EUS) have published guidelines for the investigation, diagnosis and management of hyponatraemia.⁴⁻⁵ They differentiate between acute and chronic hyponatraemia and categorise severity. Both guidelines define hyponatraemia of onset less than 48 hours prior to presentation as acute, and consider this scenario to have less risk of osmotic demyelination following correction. In our patients, however, as is frequently the case, the onset of hyponatraemia could not be determined with certainty at presentation. The guidelines differ in their definitions of severity with the EUS guidelines categorising a serum sodium of <125mmol/L as severe compared with the ESE definition of <120mmol/L. The three cases described here are thus severe hyponatraemia by either definition.

Severe hyponatraemia is often associated with cerebral oedema causing neurological symptoms ranging from nausea and headache to seizure and death.⁴⁻⁵ Both guidelines recommend treatment of severe,

symptomatic hyponatraemia with 3% hypertonic saline, with the immediate goal of raising the serum sodium by 4-6mmol/L. Following this, they recommend that over the next 24 hours serum sodium should not be elevated by more than a total of 10mmol/L to minimise risk of osmotic demyelination syndrome. Chronic hyponatraemia is associated with brain adaptations to a hypotonic extracellular environment. Rapid correction of serum sodium in chronic, severe hyponatraemia has been shown in animal and clinical studies to be associated with demyelination in pontine and extrapontine brain centres, leading to devastating neurological consequences⁶⁻⁸. Thus, both the ESE and EUS guidelines suggest that if there is uncertainty around the timing of onset of hyponatraemia, as in our first two cases, the limits to correction as cited above should be applied. Given the known acute nature of the hyponatraemia developed by Patient 3, it was judged to be safe to allow for a more rapid correction of sodium in her case⁹.

In patients with PP who have acutely ingested large volumes of hypotonic fluid, a reduction in serum osmolality results in ADH suppression. This, as well as reversal of non-osmotic stimuli of ADH secretion and underlying impaired sodium reabsorption due to renal medullary gradient washout, can lead to free water diuresis and a rapid rise in serum sodium when fluid intake is restricted.¹ These mechanisms may explain the clinical course and rapid overcorrection observed in our three cases.

Chronicity and aetiology of hyponatraemia can be difficult to determine at the time of presentation. In our first two cases, there was delay in ascertaining PP as the underlying cause and the rapid sodium overcorrection was of great concern. While the clinical phenomenon of large volume diuresis contributing to sodium overcorrection is recognised, there is a lack of randomised controlled trial data to guide explicit

recommendations as to how this should be mitigated. There have been case series and retrospective cohort studies that suggest intravenous desmopressin could be used concurrently with hypertonic saline, or, at the time when the initial 4-6mmol/L increase in sodium has been achieved, to prevent overcorrection¹⁰⁻¹¹. In the scenario of established sodium over-correction, animal studies of osmotic demyelination and a small number of clinical case reports have shown reversal of clinical features of osmotic demyelination with sodium re-lowering¹²⁻¹⁴. This can be achieved with intravenous desmopressin in combination with hypotonic fluid administration. Due to lack of evidence there is discrepancy between the guidelines regarding desmopressin dosing and frequency, as well as hypotonic fluid volume and rate of administration required to achieve sodium re-lowering. It is thus prudent to seek advice from physicians experienced in the management of this challenging clinical situation.

REFERENCES: *(Supply no more than 20 references. Style and punctuation should conform to the Vancouver format. List all authors when six or fewer; when seven or more list the first six and add et al. The issue number should not be quoted. Website references – treat as other reference. In the text, references should be cited using superscript Arabic numerals in the order in which they appear. If cited only in tables or figure legends number them according to the first identifications of the table or figure in the text. In the reference list, the references should be numbered and listed in order of appearance in the text.)*

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Figure Legend:

Figure 1: Venous blood gas sodium and urine output vs time until 50 hours from IV treatment.

a. Patient 1: Initial VBG sodium 112mmol/L. IVT: 20mL 3% normal saline; solute load 10mmol over 1 hour. Correction to 130mmol/L at 7 hours post IVT. Urine output 4750mL in 7 hours post IVT. 2ug DDAVP administered IV at 7hrs and again at 10hrs, with reduction in urine output and relowering of sodium with concurrent 5% dextrose. Second peak of serum sodium 131mmol/L at 32 hours post IVT. Urine output of 2835mL over one hour at 34 hours post IVT.

b. Patient 2: Initial VBG sodium 114mmol/L. IVT: 794mL 0.9% normal saline over 12 hours (varying rates). Solute load 122mmol (in 12 hours). Correction of sodium to 135mmol/L at 12 hours post IVT. Urine output 5985mL in 12 hours post IVT. 1ug DDAVP administered IV at 12hrs, with reduction in urine output and relowering of sodium with concurrent 5% dextrose. Data for urine output incomplete after 31 hours post IVT.

c. Patient 3: Initial VBG sodium 113mmol/L. IVT: 250mL 3% normal saline over 2 hours. Solute load 128mmol (in two hours). Urine output 4930mL in 18 hours post IVT. Correction of sodium to 136mmol/L at 18 hours post IVT. Data for urine output incomplete after 41 hours post IVT.

DDAVP: desmopressin, IVT: intravenous therapy, Na: sodium, VBG: venous blood gas

Acronym list

ADH Anti-diuretic hormone

ESE European Society of Endocrinology

EUS Expert panel based in the United States

PP Primary polydipsia

SIADH Syndrome of Inappropriate Anti-diuretic Hormone

TSH Thyroid Stimulating Hormone

WORD LIMIT: 1,500 words

ACKNOWLEDGEMENTS: (if applicable); include external contributors, their affiliations and institutions.)

ABBREVIATIONS: (Put in full when first used, hereafter use acronyms.)

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MEASUREMENTS: (All measurements must be given in SI units.)

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