

Persistent syndrome of inappropriate antidiuretic hormone secretion following traumatic brain injury

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Summary

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) can occur following traumatic brain injury (TBI), but is usually transient. There are very few case reports describing chronic SIADH and all resolved within 12 months, except for one case complicated by meningo-encephalitis. Persistent symptomatic hyponatremia due to chronic SIADH was present for 4 years following a TBI in a previously well 32-year-old man. Hyponatremia consistent with SIADH initially occurred in the immediate period following a high-speed motorbike accident in 2010. There were associated complications of post-traumatic amnesia and mild cognitive deficits. Normalization of serum sodium was achieved initially with fluid restriction. However, this was not sustained and he subsequently required a permanent 1.2 l restriction to maintain near normal sodium levels. Multiple episodes of acute symptomatic hyponatremia requiring hospitalization occurred over the following years when he repeatedly stopped the fluid restriction. Given the ongoing nature of his hyponatremia and difficulties complying with strict fluid restriction, demeclocycline was commenced in 2014. Normal sodium levels without fluid restriction have been maintained for 6 months since starting demeclocycline. This case illustrates an important long-term effect of TBI, the challenges of complying with permanent fluid restrictions and the potential role of demeclocycline in patients with chronic hyponatremia due to SIADH.

Learning points:

- Hyponatraemia due to SIADH commonly occurs after TBI, but is usually mild and transient.
- Chronic hyponatraemia due to SIADH following TBI is a rare but important complication.
- It likely results from damage to the pituitary stalk or posterior pituitary causing inappropriate non-osmotic hypersecretion of ADH.
- First line management of SIADH is generally fluid restriction, but hypertonic saline may be required in severe cases. Adherence to long-term fluid restriction is challenging. Other options include oral urea, vasopressin receptor antagonists and demeclocycline.
- While effective, oral urea is poorly tolerated and vasopressin receptor antagonists are currently not licensed for use in Australia or the USA beyond 30 days due to insufficient long-term safety data and specific concerns of hepatotoxicity.
- Demeclocycline is an effective, well-tolerated and safe option for management of chronic hyponatraemia due to SIADH.

Background

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is associated with various clinical situations and frequently arises due to CNS pathology. Clinical features are non-specific, and depend upon the absolute serum sodium level and rate of development. Initial symptoms may include nausea, malaise, headache, lethargy and mild cognitive deficits, and in severe cases may progress to seizures, cardio-respiratory distress and coma (1). Essential diagnostic criteria include low serum osmolality (<280 mmol/kg) with an inappropriately high urine osmolality (>100 mmol/kg) and urine sodium concentration (>30 mmol/l). Additional features include clinical euvolemia, absence of adrenal, thyroid, pituitary or renal insufficiency, and/or use of diuretic agents (1) (2). Hyponatraemia due to SIADH is a well-recognised complication of traumatic brain injury (TBI) and has previously been described in both children and adults, although it is usually mild and transient. This is the first reported case to our knowledge of chronic SIADH due to TBI, uncomplicated by meningo-encephalitis. It is a rare but important presentation of a common disease that clinicians should be aware of when evaluating a patient with hyponatraemia, and highlights a possible long-term effect of TBI on the endocrine system. Management is challenging due to its longevity and although effective, long-term fluid restriction in such scenarios is often accompanied by poor adherence as exemplified by our case. Our discussion encompasses alternate management strategies for chronic SIADH, in particular the role of demeclocycline.

Case presentation

A 32-year-old man was admitted to The Alfred Hospital, Melbourne, Australia in December 2010 following a high-speed motorcycle accident with an initial Glasgow coma score (GCS) of 14. In addition to a TBI, he sustained C4 to C7 ligamentous damage, multiple fractures of the pelvis, ribs, sternum and facial bones, and significant soft-tissue trauma. By day 2 of admission, his GCS had normalised. Despite a mild TBI and the absence of structural damage on CT and MRI brain imaging, he developed post-traumatic amnesia and subjective long-term cognitive deficits preventing him from returning to work. Formal neuropsychiatric evaluation and functional imaging was not performed, so there was no objective evidence of permanent brain damage. The GCS was introduced as a method for determining the severity of brain dysfunction

6 h after head trauma and cannot predict long-term cognitive function, so it likely underestimated the impact of this injury on our patient's long-term cognitive function. On day 3 of his admission, he developed hyponatremia consistent with SIADH: serum sodium 117 mmol/l (reference range: 135–143), serum osmolality 247 mmol/kg (280–300), urine sodium 112 mmol/l (>30) and urine osmolality 920 mmol/kg. He was symptomatic with nausea, but cognition remained intact with a GCS of 15. He was clinically euvolemic with a urine output of 100 ml/h and an overall minor positive net external fluid balance (total daily fluid input 2600 ml, total daily fluid output 2450 ml). His thyroid function was normal: fT_4 15.5 pmol/l (9.1–19.6), TSH 2.29 mU/l (0.3–5), and repeated cortisol levels were robust: day 4 admission 0820 h cortisol 357 nmol/l (100–540), day 6 admission 0910 h cortisol 583 nmol/l. An MRI pituitary was also performed, which was normal. An insulin tolerance test was not performed as repeated cortisol levels were considered sufficient especially a value >550 nmol/l. Furthermore, it might be unsafe to perform in a head-injured patient at least in the acute setting. He was not taking any medications at the time of presentation and denied a history of illicit drug use. Temporary 1.5 l fluid restriction normalized sodium levels. Following discharge to a rehabilitation unit he experienced recurrence of moderate hyponatremia, again consistent with SIADH, requiring long-term fluid restriction. Over the subsequent 3 years, he was advised to adhere to 1.2 l fluid restriction, which only maintained serum sodium levels of 128–130 mmol/l. Adherence was difficult, resulting in nine hospital admissions due to worsening hyponatremia with symptoms including nausea and malaise. On each occasion biochemistry remained consistent with SIADH and serum sodium improved with tight fluid restriction as low as 500 ml daily. Psychogenic polydipsia is an important consideration in those presenting with recurrent euvolaemic hyponatraemia, but the fluid restriction required in this case to achieve normonatremia was severe and inconsistent with a diagnosis of psychogenic polydipsia. There was no evidence of hypopituitarism, malignancy, intercurrent pulmonary disease or nervous system disorders during this time, and pain was well controlled on paracetamol and buprenorphine. The etiology of his chronic SIADH was considered to be most likely secondary to prior TBI. He was most recently admitted in September 2014, presenting with several hours of nausea, malaise and anorexia in the context of not adhering to his fluid restriction. He was clinically euvolaemic. Biochemistry was consistent with SIADH:

serum sodium 119 mmol/l, serum osmolality 253 mmol/kg, urine sodium 119 mmol/l, urine osmolality 764 mmol/kg, TSH 0.55 mU/l (0.3–5), fT₄ 12.6 pmol/l (9.1–19.6), cortisol at 0600 h 347 nmol/l (100–540). Serum sodium improved with a daily 500 ml fluid restriction.

Investigation

Please refer to the preceding case description.

Treatment

Given the ongoing nature of the hyponatremia and difficulty adhering to long-term fluid restriction, demeclocycline 300 mg twice daily was commenced. Fluid restriction was relaxed initially to 2 l daily and after three days ceased altogether.

Outcome and follow-up

He is progressing well after 6 months of demeclocycline therapy, now at a reduced dose of 150 mg twice daily without any adverse effects. Serum sodium levels have been consistently normal (136–139 mmol/l) for the first time since initial injury. While spontaneous resolution of hyponatraemia may have coincided with institution of demeclocycline, it is highly unlikely given the problem had persisted for so many years. Liver function has been checked regularly and remains normal.

Discussion

Various degrees of hypopituitarism are well described after TBI (3). Transient hyponatremia due to SIADH is also common in patients who have suffered TBI. Born *et al.* (4) evaluated 109 patients with a GCS \leq 7 in the first 24 h after a severe head injury. Patients were followed during their admission, with 36 developing SIADH at various time points following their injury up until day 19. While SIADH is recognised as a common early complication of TBI, it rarely persists or recurs. There are very few published reports of patients suffering from persistent or recurrent hyponatremia due to chronic SIADH after TBI (5) (6) (7). Kumar *et al.* (5) described a 38 year-old man who presented 1 year after TBI with SIADH complicated by seizures, which quickly responded to fluid restriction. There were no further reported seizures, although additional follow-up information was not provided. Another case report by Chang *et al.* (6) described a 48-year-old patient who

suffered from recurrent symptomatic hyponatremia due to SIADH following a head injury. This patient experienced three episodes of hyponatremia requiring multiple hospital admissions on days 4, 75 and 125 post-injury. These episodes lasted 28, 22 and 14 days respectively, measured from the day of onset to the day of highest measured sodium level. Initial hyponatremia management included hypertonic saline and fluid restriction, with the two subsequent episodes managed with fluid restriction alone. The patient suffered no further hyponatremic episodes beyond the time reported. Finally, Graziani *et al.* (7) described a 47-year-old man who developed SIADH after suffering meningoencephalitis following a severe head injury. Initial fluid restriction was unsuccessful and tolvaptan, a vasopressin receptor antagonist was administered, resulting in rapid correction of sodium levels. Tolvaptan was ceased after 2 months of stable sodium levels, but complicated by immediate recurrence of hyponatremia. Reintroduction of tolvaptan quickly normalized sodium levels and the patient had continued treatment for 6 months at the time of publication. The pathophysiological mechanisms responsible for SIADH after TBI remain uncertain (2) (5). Proposed mechanisms include pituitary stalk or posterior pituitary injury leading to inappropriate non-osmotic hypersecretion of ADH (2). Presumably this is usually a transient effect as hyponatremia resolves after a short duration of fluid restriction in most patients. As demonstrated by our case, it seems permanent selective damage to these structures is possible. The management strategy of hyponatraemia expressed in recent expert guidelines should be based on the underlying cause, the presence of neurological symptoms which helps indicate severity, and the speed at which onset of hyponatraemia occurred (8) (9). Acute symptomatic hyponatraemia regardless of the cause is best corrected with hypertonic (3%) saline given either via bolus or continuous i.v. infusion (8) (9). Treatment of chronic hyponatraemia or hyponatraemia of indeterminate duration should involve a controlled and limited correction to avoid the neurological sequelae of osmotic demyelination (8) (9). For most cases of mild-to-moderate SIADH, fluid restriction is regarded as first line therapy (8). Long-term fluid restriction is occasionally required but often complicated by poor adherence, especially when cognitive damage has been sustained. In cases of SIADH where the cause of hyponatraemia persists and fluid restriction is ineffective or impractical, pharmacological therapy should be considered. Oral urea can increase urinary solute excretion and induce an osmotic diuresis (8) (10). This has shown promising results in the treatment of

long-term SIADH with recurrent hyponatremia, but is generally poorly tolerated due to its unpleasant taste (10). Vasopressin receptor antagonists are effective for euvolaemic and hypervolaemic hyponatremia (The Australian Register of Therapeutic Goods: <https://www.tga.gov.au/product-information-pi>). However, due to a lack of sufficient long-term safety data and specific concerns related to hepatotoxicity, the currently available oral agent, tolvaptan, is currently not licensed in Australia or the USA for longer than 30 days (The Australian Register of Therapeutic Goods: <https://www.tga.gov.au/product-information-pi>). Demeclocycline, a tetracycline antibiotic that inhibits the action of antidiuretic hormone in the renal distal tubule has a well-established role in the management of chronic hyponatremia, but the authors are not aware of any published data on its role in SIADH following TBI (8) (10). The recommended treatment dose is 600–1200 mg/day (8). This case highlights a possible long-term effect of TBI on the endocrine system, the challenges of complying with a long-term fluid restriction and the potential role of demeclocycline in patients with chronic hyponatremia due to SIADH from TBI.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent has been obtained from the patient for publication of the submitted article.

Author contribution statement

Michael Dick – final year medical student from Auckland University who worked with the Department of Endocrinology and Diabetes at Alfred Health for a 6 week medical elective in 2014. He was intimately involved in the care of the patient while an inpatient and wrote up the case and

discussion. Sarah Catford – Endocrinology advanced trainee who looked after the patient while an inpatient and contributed significantly to the case report and discussion. Kavita Kumareswaran – Endocrinologist and supervisor of Michael Dick while on rotation. She assisted with editing of the case and discussion. Peter Shane Hamblin – Endocrinology consultant on ward service at the time of patient admission and therefore he was primarily responsible for the patient. He initiated and planned write up of the case given its noteworthy nature and assisted with editing of the case and discussion. Duncan Topliss – Director of Endocrinology and Diabetes, Alfred Health. He was involved in the management of the patient while an inpatient, specifically regarding the use of demeclocycline. He also assisted with editing of the case and discussion.

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