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Posterior pituitary dysfunction following traumatic brain injury: review

Roxana Maria Tudor[1] · **Christopher J. Thompson**[1]

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Abstract

Neurohypophysial dysfunction is common in the first days following traumatic brain injury (TBI), manifesting as dysnatremia in approximately 1 in 4 patients. Both hyponatremia and hypernatremia can impair recovery from TBI and in the case of hypernatremia, there is a significant association with excess mortality. Hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIAD) is the commonest electrolyte disturbance following TBI. Acute adrenocorticotropic hormone (ACTH)/cortisol deficiency occurs in 10–15% of TBI patients and can present with a biochemical picture identical to SIAD. For this reason, exclusion of glucocorticoid deficiency is of particular importance in post-TBI SIAD. Cerebral salt wasting is a rare cause of hyponatremia following TBI. Hyponatremia predisposes to seizures, reduced consciousness, and prolonged hospital stay. Diabetes insipidus (DI) occurs in 20% of cases following TBI; where diminished consciousness is present, appropriate fluid replacement of renal water losses is occasionally inadequate, leading to hypernatremia. Hypernatremia is strongly predictive of mortality following TBI. Most cases of DI are transient, but persistent DI is also predictive of mortality, irrespective of plasma sodium concentration. Persistent DI may herald rising intracranial pressure due to coning. True adipsic DI is rare following TBI, but patients are vulnerable to severe hypernatremic dehydration, exacerbation of neurologic deficits and hypothalamic complications, therefore clinicians should be aware of this possible variant of DI.

Keywords Traumatic brain injury (TBI) · Posterior pituitary dysfunction · Hyponatremia · Syndrome of inappropriate antidiuretic hormone secretion (SIAD/SIADH) · Diabetes insipidus (DI) · Adipsic diabetes insipidus

Introduction

Traumatic brain injury (TBI) has been recognised to cause posterior pituitary dysfunction for many years. Diabetes insipidus has been described following brain injury on many occasions, with initial reports dating back to 1957 [1]. Soon after the initial descriptions of syndrome of inappropriate antidiuretic hormone secretion (SIAD) in 1957 [2], reports appeared in the literature of hyponatremia occurring as a complication of traumatic brain injury [3]. Awareness of posterior pituitary dysfunction following TBI predated that of anterior pituitary dysfunction by many decades [4] and management of hyponatraemia and diabetes insipidus is part of routine protocols following TBI [5].

In recent years, hypernatremia in particular has been associated with worse prognosis and increased mortality following TBI [6–8]. Hyponatremia following TBI is less strongly associated with poor prognosis, though retrospective studies show that all-cause hyponatraemia is associated with longer hospital stay and that symptoms of cerebral irritation are related to more severe biochemical hyponatremia [9].

Posterior pituitary dysfunction contrasts with anterior pituitary dysfunction in that dysnatremias occur most commonly in the immediate post-TBI period and almost always completely recover in survivors of head injury. Hyponatremia rarely persists [10], whereas only 6% of long term survivors of TBI have objective evidence of diabetes insipidus on formal testing, most of whom have mild symptoms only [11].

Because posterior pituitary dysfunction occurs early after TBI, diagnostic and therapeutic approaches are focussed on in-patients in the immediate aftermath of admission or neurosurgical intervention.

✉ Roxana Maria Tudor
roxanamariatudor@beaumont.ie

[1] Academic Department of Endocrinology, Beaumont Hospital/RCSI Medical School, Dublin, Ireland

In this article we will discuss the approach to patients with hyponatremia and diabetes insipidus following TBI.

Hyponatremia in TBI

Epidemiology

Hyponatremia is the most common electrolyte abnormality following TBI, with approximately 20% of survivors having a decreased plasma sodium concentration of < 135 mmol/l, in the week following brain insult [12]. Retrospective [9] and prospective data from our unit [6, 13] indicates consistently that 10–15% of the patients with TBI develop significant hyponatremia (Na < 130 mmol/l).

Aetiology of hyponatraemia

It is crucial to correctly identify the causation of hyponatremia, as management of the condition is aetiology-specific. There is a wide differential for the diagnosis of hyponatremia in TBI, which is summarised in Table 1.

The clinical approach to the etiological diagnosis of hyponatraemia is usually centred around the assessment of the patient's blood volume status. This may be challenging in a patient on a Neurosurgical ITU, who may be on intravenous fluids, vasopressors and other agents such as mannitol or loop diuretics. However fluid balance is usually accurately monitored in intensive care and central venous pressure (CVP) measurements may be available to assist diagnosis, so a decent estimation of blood volume status can usually be calculated.

Most studies concur that the commonest cause of hyponatremia following TBI is SIAD. A large retrospective study indicated that SIAD was the cause of post-TBI hyponatremia in 60% of cases [9], and a number of prospective studies have confirmed this, in both adults and children [10, 13–15]. Most cases of SIAD are diagnosed in the first 48 h following TBI, with rare cases reported up to 18 days following head trauma [10].

The key diagnostic criteria for SIAD, which were originally defined in 1967 by Bartter and Scwartz, are summarised in Table 2. They remain essentially unchanged today and depend upon the identification of euvolemic hyponatremia, with inappropriately concentrated urine, elevated urinary Na excretion (> 20–30 mmol/l) with the exclusion of glucocorticoid deficiency and severe hypothyroidism [16, 17]. We will argue later in this paper that exclusion of ACTH/cortisol deficiency is of particular importance following TBI.

In TBI patients the major differential diagnosis of SIAD is acute glucocorticoid deficiency. Good quality prospective studies have shown that acute ACTH deficiency can occur in 15–20% of patients following TBI [14, 15, 18]. The consequent cortisol deficiency may be severe enough to present with severe hyponatraemia which biochemically mimics SIAD [6, 19]. Thus exclusion of cortisol deficiency

Table 2 Essential diagnostic criteria for SIAD [26]

Serum sodium < 135 mmol/l
Decreased effective plasma osmolality (Posm < 275 mOsm/kg)
Inappropriate urine concentration in the context of plasma hypo-osmolality (Uosm > 100 mOsm/kg)
Clinical euvolemia
Increased urinary sodium excretion > 30 mmol/l with normal dietary salt intake and water intake
Exclusion of glucocorticoid and thyroid hormone deficiency
No recent use of diuretic agents

SIAD syndrome of inappropriate antidiuretic hormone secretion, *Posm* plasma osmolality, *Uosm* urine osmolality

Table 1 Differential diagnosis of hyponatremia following TBI based on the fluid status

Fluid status	Clinical features	Urine sodium < 30 mmol/l	Urine sodium > 30 mmol/l
Hypovolemic	Tachycardia Hypotension Decreased skin turgor or dry mucous membranes Low CVP Raised urea	Dehydration Vomiting	Cerebral salt wasting (rare) Inadequate IV fluids Diuretic use
Euvolemic (most common)	Normal heart rate Normal blood pressure Normal CVP	SIAD with fluid restriction	SIAD Acute ACTH deficiency SSRI use
Hypervolemic	Raised JVP Peripheral oedema Bibasal crackles	Injudicious use of IV fluids Congestive heart failure Hepatic failure/cirrhosis	Renal failure

TBI traumatic brain injury, *CVP* central venous pressure, *SIAD* syndrome of inappropriate antidiuretic hormone secretion, *ACTH* adrenocorticotropic hormone, SSRI selective serotonin reuptake inhibitors, *JVP* jugular venous pressure

is essential when approaching a patient with apparent SIAD following TBI.

A large carefully conducted prospective study has suggested that subtle and often transient ACTH/cortisol deficiency may be even commoner in the immediate few days after head injury. Using daily measurements of 09:00 h plasma cortisol, Hannon et al. demonstrated that 80% of patients had inappropriately low plasma cortisol concentrations (< 300 nmmol/l, 10.9 mg/ml) in the week following TBI, which was in contrast to control patients undergoing major abdominal surgery. The changes were not explainable by alterations in plasma cortisol binding globulin (CBG) or albumin concentrations, which remained unchanged. Of the 15% of TBI patients who developed hyponatraemia with an SIAD-like biochemical picture, 80% responded to intravenous hydrocortisone, with normalisation of plasma sodium concentration [6].

A recent large prospective study of survivors of TBI in Algiers showed lower rates of hypocortisolaemia, at 21%, using a cut-off of 276 nmol/l for 09:00 h plasma cortisol [20]. However, the patients in the Algerian cohort had a single serum cortisol measurement during the acute post-injury period. Data from Hannon et al. indicates that, as the timing of cortisol deficiency is very variable, multiple testing is necessary to identify ACTH/cortisol deficiency [6].

As the majority of cases of ACTH deficiency are transient and mild, it could be argued that screening is not justified. However, as two large prospective studies have shown that moderate to severe ACTH deficiency is predictive of mortality [6, 20], hydrocortisone therapy is potentially lifesaving. It therefore seems worthwhile to screen for cortisol deficiency in patients who develop hyponatremia post-TBI. Patients who have hypotension or hypoglycaemia in addition to hyponatremia may be more likely to be ACTH deficient [4, 21, 22].

The logistics of screening are challenging. Insulin-induced hypoglycaemia is inappropriate because of seizure risk and Synacthen testing would give falsely reassuring figures, as adrenal atrophy has not had time to develop. Hannon and colleagues used a 09:00 h plasma cortisol cut-off of 300 nmol/l (10.9 ng/ml), based on normative responses to major abdominal surgery, which seems a reasonable basis for testing [6].

Cerebral salt wasting syndrome (CSWS) was first described in 1950 by Peters et al. [23] and it typically presents with significant natriuresis and polyuria, which lead to hypovolemic hyponatremia. The exact pathophysiology of CSWS is uncertain, but increased circulating concentrations of natriuretic peptides have been suggested, as well as activation of the sympathetic nervous system [24]. A recent literature review identified 47 papers on CSWS, but only 15 met the selection criteria. 9 of the 15 papers were case reports. The authors noted large variations in diagnostic criteria used to define both hyponatremia and CSWS, as well as variations in the reported plasma concentrations of natriuretic hormone [25]. The authors concluded that there is no consensus on the definition of CSWS and there is therefore uncertainty concerning the contribution of CSWS to post-TBI hyponatremia. Retrospective data from our unit suggested that CSWS may have occurred in 5% of hyponatremic patients passing through our neurosurgical unit, but careful prospective monitoring of over 100 TBI patients failed to reveal any cases of CSWS [6].

It is clear that CSWS may be overdiagnosed unless care is taken to exclude a number of circumstances which are not uncommon in neurosurgical units. Intravenous fluid overload may expand plasma volume and precipitate a compensatory diuresis and natriuresis, so careful attention to fluid balance prior to the development of hyponatremia is crucial. Catecholamine release or vasopressor agents may increase renal perfusion and cause pressure natriuresis. Mannitol and diuretic administration may also complicate the diagnosis of CSWS. In all of these circumstances, the access to CVP readings will be central to confidently diagnose CSWS.

Leonard and colleagues have recommended that a number of criteria should be fulfilled before a diagnosis of CSWS is made [25]:

1. The presence of new brain pathology
2. New onset hyponatremia, validated by at least one simultaneously low serum osmolality.
3. Hypovolemia: this may be difficult to diagnose confidently in the setting of neurosurgery ITU, but CVP and blood pressure readings are essential.
4. Renal salt wasting: this must be confirmed as renal loss in excess of intake, within a timed period.

True CSWS is therefore a rare entity, the very existence of which has been challenged. A recent review has concluded that most post-traumatic hyponatremia is mediated by arginine vasopressin (AVP), rather than natriuretic hormones [12]. However, when CSWS does occur, the manifestations may be florid, with marked diuresis and natriuresis, accompanied by falling blood pressure and CVP. Treatment entails high volumes of intravenous saline; this therapy is so different from the treatment of other forms of hyponatremia, that the diagnosis of CSWS should be very carefully made [26, 27].

In its classic presentation, CSWS is clearly a distinct clinical entity from SIAD, as summarised in Table 3. It is important to differentiate between the two, as patients with CSWS will deteriorate if fluid restriction is commenced. CSWS is treated with aggressive intravenous saline replacement in order to restore circulating blood volume and body sodium [28], usually for a few days only, as the condition is invariably self-limiting [29].

Table 3 Clinical and biochemical features of CSWS vs. SIAD

	Cerebral salt wasting syndrome	SIAD
Mechanism	Excess water and sodium excretion	Excess water retention due to uncontrolled AVP production
Volume status	Hypovolemic	Euvolemic
Urine volume	Polyuria	Normal
Plasma sodium	Hyponatremia	Hyponatremia
Posm	Low	Low
Uosm	High	High
Urine Na	High	High
Management	IV fluids	Fluid restriction

CSWS cerebral salt wasting syndrome, *SIAD* syndrome of inappropriate antidiuretic hormone secretion, *AVP* arginine vasopressin, *Posm* plasma osmolality, *Uosm* urine osmolality

A number of therapeutic interventions can result in hyponatremia during the management of TBI. Diuretic use or inadequate fluid resuscitation may lead to hypovolemic hyponatremia. The use of the antiseizure medication carbamazepine may cause SIAD. Conversely, the administration of hypotonic intravenous fluids and the injudicious use of Desmopressin could precipitate dilutional hyponatremia. Data has suggested that 21% of hyponatremia in TBI patients is iatrogenic [19].

Effects of hyponatremia

As most hyponatremia following TBI is of acute onset, it is particularly likely to cause neurological symptoms, as there is no time for the brain to develop compensatory mechanisms. This is especially true where coexistent morbidities such as brain injury, hypoxia and abnormal brain perfusion may further enhance cerebral irritation. Animal models of brain injury have demonstrated that hyponatremia has been associated with swelling of astrocyte foot processes, increase in contusion volume and downregulation of aquaporin-4, suggesting that hyponatremia may directly mediate some of the secondary damage associated with TBI [30].

If hyponatremia is severe and not corrected, it can progress to cerebral oedema, raised intracranial pressure and coning. Data from our unit suggest that the signs of cerebral irritation are related to more severe hyponatremia [9].

Diminished conscious level, seizures and, on a long term, poor engagement with rehabilitation are well known consequences of hyponatremia following TBI. However, it is important to emphasise that current data indicates that hyponatremia in neurosurgical patients has not been implicated in excess mortality [9].

Treatment of hyponatremia post TBI

The evidence base for the treatment of hyponatremia following TBI per se is negligible, therefore the indications for treatment and preferred mode of therapy must be inferred from other situations and applied with good clinical acumen. Acute symptomatic hyponatremia is a medical emergency with a high mortality, and in TBI, where intracranial pressure may be increased as a result of the cerebral insult, it should be treated with urgency. Current guidelines have advocated the use of bolus hypertonic (3%) saline, rather than the traditional continuous intravenous infusion, in order to decrease intracerebral pressure more effectively [26].

If the onset of hyponatremia is known with certainty to be less than 48 h, which is often the case in neurotrauma, the risk of osmotic demyelination with correction of hyponatremia is small, and no limits need be placed on the rate of correction of plasma sodium [26, 31]. Where the development of hyponatremia exceeds 48 h or is unknown, it is safer to aim for an initial rise in plasma sodium of 4–6 mmol/l over the first 6 h, with a slower rise to a target of 8–12 mmol/l in the first 24 h [26].

Where hyponatremia is mild and not associated with neurological symptoms, no intervention is needed, as hyponatremia invariably normalises over 5–10 days, even without treatment [9].

Moderate hyponatremia with mild symptoms requires the most careful consideration. All current guidelines recommend fluid restriction as first line therapy [26, 32], but we know that the response to fluid restriction in clinical practice is disappointing [33] and many neurosurgeons are reluctant to allow fluid restriction in their ITU departments.

European guidelines have recommended the use of urea therapy [32] and non-randomised retrospective studies [34], including patients with neurosurgical conditions [35] have suggested that this is a safe and effective therapy. However a recent Cochrane analysis has found no evidence base for its use [36]. There is a clear need for prospective controlled trials using this modality [37].

Tolvaptan, the vasopressin receptor antagonist, has also not been tested formally in the post TBI setting. A single case report has described a patient who responded very

rapidly to Tolvaptan, and cautioned that low doses of the drug should be used, in order to avoid overcorrection and reduce the risk of osmotic demyelination [38].

In the absence of a strong evidence base, good clinical judgement should determine physician choices for the treatment of hyponatremia following TBI.

If SIAD rarely persists after the initial injury, it usually reflects confounding factors such as post-traumatic hydrocephalus or the prescription of drugs such as selective serotonin reuptake inhibitors (SSRIs) or anti-seizure medication. In a retrospective study of 102 patients, only one had hyponatremia which persisted into the chronic phase, after 17 months of follow-up [10].

Diabetes insipidus

Epidemiology

Because of the unique anatomy of the pituitary gland and the intricacies of its vascular supply, the pituitary stalk is particularly vulnerable to damage during brain trauma. Diabetes insipidus (DI) has been recognised as an early complication of TBI for many years.

The reported incidence of DI after TBI varies according to selection criteria and diagnostic paradigms and estimates range from 3 to 50% [6, 10, 21, 22, 39–42]. Most well conducted prospective series, with tight inclusion and diagnostic criteria, estimate the incidence of DI at 15–28% [6, 10, 21, 22, 39, 41]. The sole study to record a low incidence of DI identified severe cases only, associated with marked hypernatremia. It seems likely that these investigators have underestimated the true incidence of DI, given the significant discrepancy between their figures and the rest of the data available in the literature [40].

Diagnosis of DI following TBI

Symptoms of diabetes insipidus usually manifest between 4 and 7 days following TBI. As the patient may not be conscious, the main symptom to alert the clinician is polyuria; even a conscious patient may not complain of thirst because of cognitive impairment due to TBI.

The patient recovering from TBI is obviously not a candidate for water deprivation testing, and most authorities recommend the application of the Seckl and Dunger criteria [43], which were originally introduced to aid the diagnosis of DI following hypophysectomy.

These criteria, after the exclusion of hyperglycaemia or mannitol therapy, include:

1. Polyuria (urine volume > 2 ml/kg/h or > 300 ml/h in two consecutive hours)
2. Hypotonic urine (Urine osmolality < 300 mOsm/kg)
3. Increased plasma osmolality > 300 mOsm/kg. Plasma sodium is more reliable for diagnosis in the acute phase; plasma sodium concentration > 145 mmol/l along with polyuria are suggestive of DI.

There is no role for the incorporation of measurement of plasma AVP or plasma copeptin.

The risk of developing acute DI has been shown to be closely related to both severity of trauma (as measured by Glasgow Coma Scale) and the presence of cerebral oedema on Computed Tomography of brain [10]. In general, DI develops in patients with more severe trauma [21].

Consequences of DI

It is important to recognise DI as soon as polyuria develops. Patients on ventilators and conscious patients with cognitive impairment cannot respond to increased free water clearance with adequate replacement fluid intake and therefore need prompt treatment with Desmopressin and intravenous (IV) fluids.

Patients with DI usually have intact thirst and appropriate drinking behaviour [44], but after TBI they may develop severe hypernatremia due to failure to replace urinary water losses. This is extremely serious as hypernatremia has been strongly linked to increased mortality following TBI. A large retrospective analysis from data collected as part of the Nationwide Inpatient sample in the USA found that in a cohort of 85,000 patients with TBI, the 4542 patients with hypernatremia had higher mortality and higher likelihood of placement of tracheostomy or gastrostomy tubes [8]. In addition, hypernatremia was associated with higher hospital costs and longer hospital stay.

The higher mortality with hypernatremia was confirmed by another large retrospective study [7] and a smaller prospective study [6]. In Hannon's prospective study, persistent DI was strongly predictive of in-patient mortality, as it was often seen as a pre-morbid event heralding the onset of rising intracranial pressure, with progression to coning and death [6]. DI is so common as a pre-fatal event, that 80% of TBI patients who are brain dead on ventilators manifest central DI [45].

In some studies, the presence of acute DI is predictive of the later development of anterior pituitary hormone deficits [6], but this has not been found in other prospective studies [10, 13, 21]. However, the association was felt to be strong enough that the presence of acute DI was included in a list of indications for formal screening for anterior pituitary dysfunction in published guidelines [46].

Natural history of DI following TBI

The vast majority of cases of post-TBI DI recover completely within 2–5 days. Careful studies conducted well after recovery from DI show that 7% of patients failed the water deprivation test, though only 2% were symptomatic [10]. Prospective studies show that the recovery occurs during the first six months after TBI [21]. Therefore, the therapeutic focus for DI is in the immediate post-TBI period.

It is worth emphasising one variant of DI. Occasionally patients will develop polyuria 2–4 days after TBI, but then progress to a period of concentration of urine and the development of hyponatremia, before finally relapsing into permanent DI. This triple phase response is thought to reflect an early contusion injury causing acute DI, followed by release of pre-formed AVP from vesicles in the termini of damaged magnocellular neurones in the posterior pituitary. The unregulated release of AVP causes transient SIAD, but as the damaged neurones undergo gliosis, permanent DI ensues [4].

The key reason to identify this variant is to avoid continued Desmopressin therapy in the SIAD phase, which may worsen hyponatremia.

Management of DI

Most cases of DI in neurosurgical patients are transient, therefore the current practice is to administer a single parenteral (subcutaneous or intramuscular) dose of Desmopressin, which is active for 6–12 h. Most frequently, only two or three doses of Desmopressin are required before DI resolves. For this reason it is usual practice not to give regular Desmopressin, but to withhold doses until polyuria returns [4]. The commonest adverse effect encountered with Desmopressin treatment is hyponatremia. It is very important to closely monitor plasma sodium concentrations after starting Desmopressin, particularly following TBI.

Hypernatremia may need specific reversal with intravenous dextrose or nasogastric water. Although the association between reversal of hypernatremia and the development of osmotic demyelination is not recognised to the same extent as with hyponatremia, cases have been reported so it makes sense not to lower plasma sodium concentration by more than 0.5 mmol/l/h, in order to avoid this disastrous development [47, 48].

A proposed diagnostic algorithm and therapeutic approach for DI is detailed in the Fig. 1.

A minority of patients will end-up using Desmopressin regularly. Oral Desmopressin should be administered in a dose that is proportional to the degree of vasopressin deficiency and efficient in controlling symptoms: a single nocturnal dose of 0.2 mg is usually sufficient to prevent nocturia in patients with partial DI, whereas those with more severe disease may need a dose of 0.2 mg twice or even three times daily [4]. Patients on long-term Desmopressin are advised to delay one dose once a week to allow aquaresis and prevent the development of dilutional hyponatremia.

Adipsic DI

Many patients develop cognitive impairment or decreased conscious levels after TBI, which compromises their ability to recognise dehydration and respond with appropriate fluid intake. They require supportive therapy until their normal homeostatic thirst mechanism returns. Rarely however, true adipsic DI can occur, due to infarction of the anterior hypothalamus, where the osmoreceptor nuclei are sited.

The syndrome is characterised by hypotonic polyuria associated with marked hypernatremia, but no sensation of thirst. Formal testing during osmotic stimulation of the neurohypophysis reveals no rise in visual analogue scale thirst ratings and poor water intake in response to hypernatremia [44, 49]. Patients are able to generate very high plasma concentrations of AVP in response to hypotensive stimuli, which indicates an osmoreceptor lesion rather than damage to the posterior pituitary [50].

Although this is a rare syndrome it is worthwhile recognising, as careful management of Desmopressin and fluid intake is needed to normalise plasma sodium. In addition patients with adipsic DI have a high incidence of other hypothalamic dysfunctions, including obesity, sleep apnoea and abnormal temperature regulation, so establishing a diagnosis of adipsic DI should alert the clinician to these possibilities.

Summary and conclusions

- Neurohypophysial dysfunction is common in the first days following TBI, affecting approximately 1 in 4 patients.
- The most common abnormality following TBI is hyponatremia secondary to SIAD (15–20% of the cases of the patients).
- Hyponatremia is associated with the potential development of acute complications such as seizures, reduced consciousness, coning and on a long term prolonged hospitalisation and poor rehabilitation outcomes.
- SIAD generally resolves in a matter of days. The treatment of choice is fluid restriction.
- ACTH deficiency is reported in 10% of the patients following TBI and exclusion of ACTH/cortisol deficiency is essential before making a diagnosis of SIAD.
- 15% of the patients develop DI in the first 48 h following TBI. The risk of developing DI is closely related to the severity of head trauma.

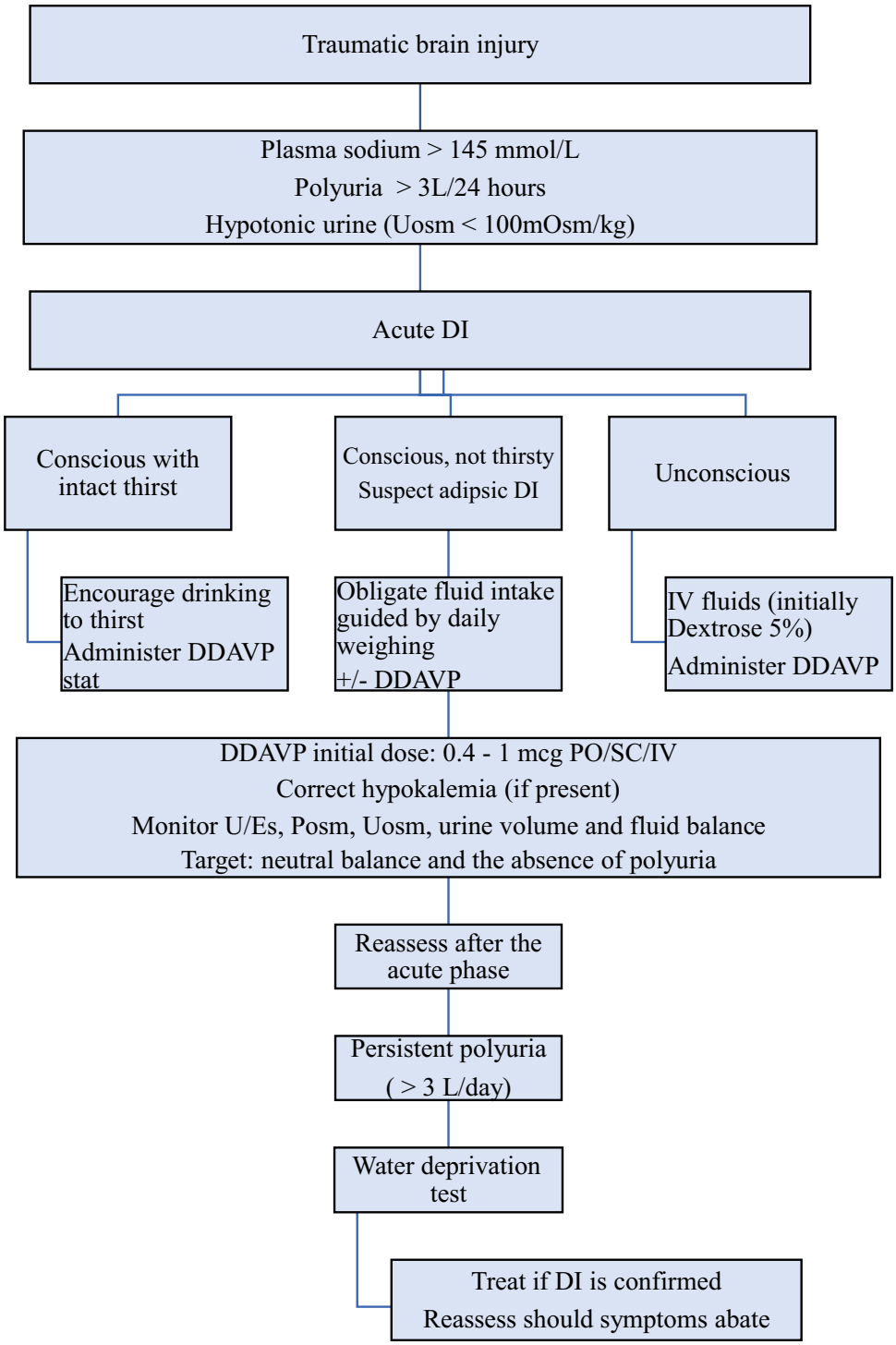

Fig. 1 Clinical algorithm for assessment of DI following TBI. *DI* diabetes insipidus, *TBI* traumatic brain injury, *DDAVP* Desmopressin, *U/Es* urea and electrolytes, *Posm* plasma osmolality, *Uosm* urine osmolality

- Recognition and treatment of hypotonic polyuria is essential, as DI is a predictor of mortality and other pituitary deficits, and hypernatremia should be treated aggressively.
- Adipsic DI is a rare clinical entity. Affected patients are vulnerable to severe hypernatremic dehydration, exacerbation of neurologic deficits and hypothalamic abnormalities.
- DI is transient in the vast majority of patients. Posterior pituitary function returns to normal within 7–10 days.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This paper does not contain any studies with human participants or animals performed by any of the authors.

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