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CLINICAL STUDY

The natural history of post-traumatic neurohypophysial dysfunction

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Abstract

Background and objectives: Posterior pituitary function remains poorly investigated after traumatic brain injury (TBI). We report the results of a study designed to prospectively define the natural history of post-traumatic diabetes insipidus (DI) and syndrome of inappropriate antidiuretic hormone secretion (SIADH) using standard reliable methodology.

Design and methods: 50 consecutive patients with severe or moderate TBI (initial Glasgow Coma Scale (GCS) score 3/15–13/15) were prospectively studied on three occasions: at the acute phase and at 6 months and at 12 months following TBI. In the acute phase, DI was diagnosed either by the presence of hypernatraemia in association with hypotonic polyuria or by the water-deprivation test (WDT) and, at 6 and 12 months by the WDT in all patients. Normative data on response to the WDT were obtained from healthy matched volunteers. Functional outcome was assessed using the Glasgow Outcome Scale (GOS).

Results: 13 patients (26%) had DI in the acute post-TBI phase, of whom nine patients recovered by 6 months and one additional patient recovered by 12 months. Of the remaining three patients with permanent DI, two had partial vasopressin deficiency. Acute-phase peak plasma osmolality correlated negatively with the initial GCS scores ($r = -0.39$, $P = 0.005$) and with the GOS scores ($r = -0.45$, $P = 0.001$). Seven patients had SIADH in the acute phase of TBI but none did at 6 or 12 months. No new cases of DI or SIADH were noted after the acute phase.

Conclusion: This prospective study shows that posterior pituitary dysfunction is common following TBI. Most cases recover completely but there is an appreciable frequency of long-term DI which can be subtle and should be recognized and managed appropriately.

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Introduction

Disorders of salt and water balance, in particular diabetes insipidus (DI) and the syndrome of inappropriate antidiuretic hormone secretion (SIADH), are common complications in the acute phase of traumatic brain injury (TBI) (1). Available information on the frequency of post-traumatic DI is principally derived by retrospective data collection (2, 3) and there have been no prospective studies attempting to accurately define the natural history of DI following TBI. Although most cases of acute post-traumatic DI seem to be transient, persistent mild DI due to partial deficiency of arginine vasopressin can be easily missed, as patients may have less-severe symptomatology and their post-traumatic clinical course is often complicated by significant neurological and cognitive disabilities and occasionally hypodipsia. In addition, DI has occasionally been reported to present in the post-acute phase of TBI (4, 5).

The lack of reliable prospective data on the natural history of post-traumatic DI prevents the development of appropriate guidelines for follow-up of post-TBI patients. With the potential of undiagnosed DI to aggravate morbidity and impede recovery and rehabilitation following TBI, such information is desirable so that timely and appropriate assessment and treatment can be provided.

We have previously reported on the prevalence of neuroendocrine dysfunction in the acute phase of TBI in a cohort of 50 patients who suffered severe or moderate TBI including a brief account of the overall frequency of acute DI and SIADH (6). In this paper, we report detailed results of 1-year prospective follow-up of posterior pituitary function in this cohort of patients to define the natural history of post-traumatic neurohypophysial dysfunction.

Subjects

Patients

50 TBI patients (38 males), with a median age of 35 years (range 15–69 years), who were admitted to the neurosurgical unit in Beaumont Hospital, Dublin,

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Ireland, over a 6-month period, were included in the study. Full details about this cohort have been reported previously (6) (Table 1). Patients had suffered severe or moderate head trauma according to the initial post-resuscitation and pre-sedation Glasgow Coma Scale (GCS) score (7). Severe injury was defined by a score of 8/15 or less and moderate injury by a score of 9/15–13/15 (8). All patients had computerized tomography evidence of brain injury (9) (Table 1). 25 patients underwent operative mass evacuation. The cause of TBI was road traffic accidents in 14 patients, falls in 26 patients, assaults in seven patients and by other means in three patients.

Exclusion criteria were as follows: patients who were moribund ($n = 5$), patients over 65 or under 15 years of age ($n = 8$), pregnant women ($n = 2$) and patients for whom informed consent was refused or could not be obtained ($n = 4$). None of the patients had established renal disease or raised creatinine ($>120\,\mu M$), were on lithium or other medications known to cause renal insensitivity to arginine vasopressin, or had diabetes mellitus, hypokalaemia or hypercalcaemia.

Controls

Dynamic posterior pituitary evaluation was performed in 27 healthy control subjects who were matched to the patient cohort for age, gender and body mass index (BMI).

Subjects and methods

The study was approved by the ethics section of the Beaumont Hospital Medical Research Committee, and all patients (or their next of kin) and controls gave informed consent.

Patients were assessed on three occasions: in the acute phase (the duration of in-hospital stay), at 6 months (during intensive rehabilitation) and at 12 months (end of intensive rehabilitation) following TBI. Functional recovery was assessed at 1 year using the Glasgow Outcome Scale (GOS) score (10) as follows: 1, death; 2, persistent vegetative state; 3, severe disability; 4, moderate disability; 5, good recovery.

Table 1 Baseline demographic and clinical characteristics of TBI patients ($n = 50$). Results are expressed as means±S.D.

Age (years)	37±14
Male/female ratio	38:12
BMI (kg/m^2)	24.3±3.8
GCS at time TBI	
Median	7/15
≤ 8/15 (*n*)	32
9/15–13/15 (*n*)	18
CT appearance	
Focal brain injury (*n*)	35
Diffuse brain injury (*n*)	15
Cerebral oedema (*n*)	33
Non-TBI general trauma (*n*)	14

CT, computed tomography.

Assessment of posterior pituitary function

In the acute phase, serial daily fluid balance and plasma sodium were obtained in all patients for the duration of their hospital stay. In patients with raised plasma sodium (>145 mM), simultaneous plasma and urine osmolalities were obtained. In patients with normal plasma sodium, further assessment was performed at 7–20 days post-TBI (median 12 days) by measuring serum and urine osmolalities following an overnight 8-h fluid deprivation and those with abnormal results (see below) had the standard observed 8-h water-deprivation test (WDT) (11, 12).

At the 6- and 12-month times, posterior pituitary function was assessed using the 8-h standard WDT. Patients receiving desmopressin were asked to withhold therapy for 48 h before the test. In the study protocol, fluids were allowed *ad libitum* until 0700 h, but the subjects had been advised to avoid alcohol for 48 h, and nicotine and caffeine for 12 h prior to the test. Patients were asked to void their bladders at 0700 h, and no fluid intake was allowed after this until 1600 h. Testing started at 0800 h. Plasma and urine osmolalities, urine volume, blood pressure and weights were measured at 0800, 1000, 1200, 1400 and 1600 h. Plasma sodium was measured at 0800 and 1600 h. Thirst scores were measured at 6 and 12 months using a visual analogue scale which has been shown to be both accurate (13) and reproducible (14). All studies were medically supervised, with the intention that studies would be stopped if subjects lost >5% of their body weight. At the conclusion of the test, patients were allowed to drink freely, and the volume of water drunk in 30 min was noted. Baseline serum samples were also obtained for measurement of urea, creatinine, calcium and potassium.

Definition of abnormalities

In view of the lack of consensus in the literature on the definition of normal response to the WDT, we studied 27 healthy controls during WDT. 24 healthy controls (89%) had peak 8-h urine osmolality exceeding 700 mOsm/kg. The three remaining healthy controls had peak urine osmolalities of 642, 682 and 694 mOsm/kg; however, all three had peak urine/plasma osmolality ratios of >2 (2.2, 2.37 and 2.32, respectively). Therefore, a normal WDT in our laboratory was defined as a peak urine osmolality of >700 mosmol/kg, or a peak urine/plasma osmolality ratio of >2.

In the immediate post-TBI period, DI was diagnosed if plasma sodium exceeded 145 mM (and plasma osmolality exceeded 300 mosmol/kg) in the presence of inappropriately dilute urine (urine/plasma osmolality ratio

<2) and polyuria of >3.5 l/24 h. In patients with normal plasma sodium, DI was diagnosed following water deprivation according to the criteria described above.

SIADH was defined as plasma osmolality <270 mosmol/kg (plasma sodium <130 mM), with a corresponding urine osmolality of >100 mosmol/kg and a spot urine sodium >40 mM, in a euvolemic patient with normal glucocorticoid secretion and thyroid function (15).

Analytical methods

Plasma and urine osmolalities were measured by depression of the freezing point method (Fiske 2400 Osmometer; Fiske, Norwood, MA, USA). Plasma sodium was measured using the ion-selective electrode method (Olympus 2700; Olympus, Tokyo, Japan). Serum urea, creatinine, calcium and potassium were measured by standard laboratory methods (Olympus 2700).

Statistics

Continuous data that were normally distributed were expressed as mean±S.D. and were compared using a two-sample *t*-test. Continuous data that were not normally distributed were expressed as medians (range) unless otherwise stated, and were analysed using the Wilcoxon rank-sum test for non-parametric measurements. Categorical data were compared using the Pearson χ^2 test. A correlation between variables was made using the Spearman's coefficient. Multifactorial logistic regression models were developed to assess the effect of appropriate variables in the presence of other confounding variables in the development of DI and SIADH. Significance of results were determined according to a two-tailed alternative hypothesis, and results were deemed significant for P values of <0.05. All of the analysis was performed using the statistical software package STATA (version 8; College Station, TX, USA).

Results

All 50 patients completed acute-phase studies, but two patients died following discharge from hospital; therefore, follow-up data at 6 and 12 months were available on 48 patients. There was a positive correlation between the initial GCS and the GOS scores ($r = 0.40$, $P = 0.005$).

Acute-phase assessment

13 patients (26%) developed DI in the acute phase of TBI (Table 2). 11 patients were diagnosed to have DI on the basis of hypernatraemia associated with hypotonic polyuria, and two patients by water deprivation (patients 8 and 9 on Table 2). The onset of DI was on days 1–3 in 11 patients, day 5 in one patient and day 11 in one patient. The range of peak plasma sodium was 146–159 mM (median, 150 mM). Univariate analysis showed acute DI to be associated with a lower GCS scale ($P = 0.018$) but logistic regression analysis showed an association of borderline significance ($P = 0.06$). Multifactorial logistic regression analysis also failed to show a significant association ($P > 0.05$) between acute DI and any of the following variables: age, BMI, gender, diffuse brain injury, the presence of cerebral oedema or operative mass evacuation. Four DI had evidence of anterior pituitary dysfunction (Table 2).

Table 2 Clinical and biochemical characteristics of patients with post-traumatic DI.

			Acute phase		6 months		12 months		
Patient/gender	**GCS score**	**GOS score**	Posm	Uosm	Posm	Uosm	Posm	Uosm	**Anterior pituitary status**
Transient DI									
1/F	7	4	305	287	298	700	297	732	ACTHD
2/M	3	3	312	372	296	815	295	794	Normal
3/M	5	1	307	252	N/A*	N/A*	N/A*	N/A*	Normal
4/M	6	3	302	249	294	755	292	744	Normal
5/F	3	5	305	167	296	952	295	900	Normal
6/M	4	5	309	195	291	702	293	734	Normal
7/F	6	3	312	290	293	786	295	721	ACTHD
8/M	10	3	301	534	296	1060	293	1273	Normal
9/M	8	4	306	418	295	840	295	810	Normal
10/M	8	4	324	180	301	499	297	956	Normal
Permanent DI									
11/F	3	2	310	201	309	390	307	436	GnTD
12/M	5	3	319	294	309	290	307	250	GnTD
13/M	7	4	307	388	303	484	305	512	Normal

GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Score; Posm, peak plasma osmolality; Uosm, peak urine osmolality; ACTHD, adrenocorticotrophic hormone deficiency; GnTD, gonadotrophin deficiency.
*Patient deceased (see text).

For the entire cohort, there was a negative association between the initial GCS scores and peak plasma osmolality ($r = -0.39$, $P = 0.005$; Fig. 1) and between the GCS scores and peak plasma sodium ($r = -0.31$, $P = 0.027$). Conversely, there was a positive correlation between the GCS score and peak urine osmolality ($r = 0.44$, $P = 0.001$; Fig. 1).

Patients with acute DI were treated initially with subcutaneous and later with oral desmopressin, with supplemental hypotonic fluids (0.45% saline) if oral intake was not possible or indequate. On discharge, oral desmopressin was prescribed to be taken as needed by the patients to control symptoms of polydipsia and polyuria. Plasma sodium was measured by the patient's general practitioner weekly for the first month after discharge, then monthly with instruction to reduce or stop desmopressin if plasma sodium fell below 135 mM and to increase the dose if plasma sodium exceeded 145 mM.

SIADH was diagnosed in seven patients (14%). None of these seven patients was on carbamazepine or other medications implicated to cause SIADH. The onset of SIADH was on day 1–3 in five patients, on day 6 in one patient and on day 10 in another patient. The range of nadir plasma sodium was 121–129 mM (median, 124 mM). One additional patient had hyponatraemia caused by acute post-traumatic adrenocorticotrophic hormone (ACTH; corticotrophin) deficiency, which was corrected by glucocorticoid therapy. Patients with SIADH were treated with fluid restriction of 1–1.5 l/24 h until plasma sodium had normalized. The median time to normalisation of plasma sodium was 7 days (range 2–26 days).

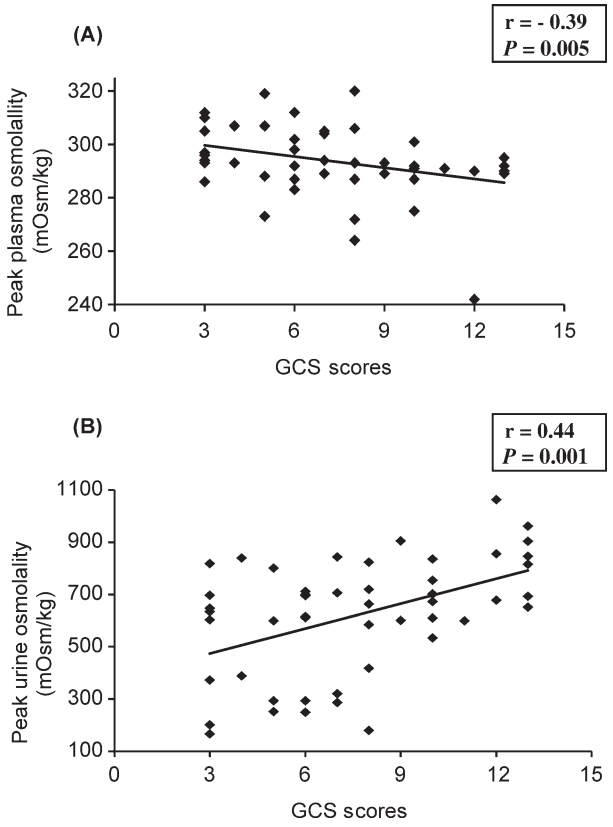

Figure 1 Correlation between the initial GCS score and peak plasma osmolality (A) and the GCS score and peak urine osmolality (B) during the acute phase of TBI.

Multifactorial logistic regression analysis failed to show an association ($P > 0.05$) between SIADH and any of the following variables: age, BMI, gender, GCS score, diffuse brain injury, the presence of cerebral oedema or operative mass evacuation.

6 month assessment

Nine patients (69%) showed recovery of vasopressin secretion as indicated by a normal WDT in eight patients and by a persistent 24-h urine output < 2.5 l in one patient who died 6 weeks after injury (Table 2). Of the four patients with persistent DI, three had evidence of partial DI (peak urine/plasma osmolality ratio of 1–2) and one patient had severe DI (peak urine/plasma osmolality ratio of < 1). All four DI patients had normal thirst appreciation and reported a history of polyuria and polydipsia responding well to desmopressin treatment, which they took regularly. The eight patients with normal WDT were asymptomatic and since discharge from hospital, five had discontinued desmopressin and three were taking it sparingly. No new cases of DI were observed.

All seven patients with acute-phase SIADH had normal plasma sodium at the 6-month assessment and no new cases of SIADH were observed.

12 month assessment

One of four patients with DI at 6 months showed recovery of vasopressin secretion, while the other three had persistently abnormal WDT (Table 2). No new cases of DI or SIADH were observed.

Association with functional outcome at 1 year

Five of the 13 patients (38.5%) with acute phase DI showed poor outcome at 1 year (GOS scores 1–3) compared with five of 37 (13.5%) patients without acute-phase DI ($P = 0.053$) There was a negative correlation between acute phase peak plasma osmolality and the GOS scores ($r = -0.45$, $P = 0.001$) and a positive correlation between acute-phase peak urine osmolality and the GOS scores ($r = 0.43$, $P = 0.002$).

Discussion

We report the results of the first study to prospectively assess sequential posterior pituitary function for 1 year following TBI using standard and reliable methodology. The data from this research help to elucidate more

clearly the natural history of post-traumatic posterior pituitary dysfunction.

The frequency of early post-traumatic DI (26%) was higher than that reported in previous retrospective studies. Wong *et al.* (2) reported DI to occur in 3.7% of neurosurgical intensive-care patients, though they did not report on the frequency of DI in the subgroup of TBI patients. In the retrospective study by Boughey *et al.* (3), the reported incidence of acute DI in TBI patients admitted to intensive care was 2.9%. However, the authors excluded patients with incomplete diagnostic data, but did not report how many patients were excluded on this basis. In the last study (3), the mean plasma sodium in the DI patients was 161 mM, suggesting that the cases identified were quite severe. Milder cases of DI may also have been missed because urine hypotonicity was defined by the arbitrary threshold of 300 mosmol/kg, a cut-off which has also been suggested by other authors (16). However, when plasma sodium exceeds 145 mM there is exuberant vasopressin secretion, resulting in maximal urine concentration (17). Therefore, a urine osmolality of 300–600 mosmol/kg, under conditions of hypernatraemia, will be inappropriately low and consistent with the diagnosis of partial DI.

Prospective assessment at 6 months using the WDT showed that most acute DI cases (nine of 13 patients, 69%) had recovered. Three of the four patients with persistent DI at 6 months had partial vasopressin deficiency, manifested by partial, but suboptimal, urine concentration in response to dehydration. As partial vasopressin deficiency may be associated with less-severe symptomatology, cases of post-traumatic DI may be missed unless patients are formally assessed. One additional patient showed recovery of vasopressin secretion by 12 months, while no new cases of DI was diagnosed after the acute phase. The overall prevalence of permanent DI after TBI was 6%, which is higher than that suggested by some authors (18, 19). The reported prevalence of post-traumatic DI, in recently published studies of patients in the chronic phase of TBI, was 0–4% (20–22). However, there studies were designed primarily to investigate anterior pituitary function and posterior pituitary evaluation was based on symptoms and/or random measurements of plasma and urine osmolalities rather than by the gold-standard WDT. By contrast, Bohnen *et al.* (23) reported DI to occur in eight of 38 patients (21%), 5 weeks following mild TBI; a much higher fig. than in our cohort. However, the authors defined DI on the basis of a plasma osmolality of >295 mosmol/kg and urine osmolality of <1000 mosmol/kg, cut-offs which are too liberal and likely to result in overdiagnosis.

The lack of systematic prospective studies on post-traumatic DI is surprising considering that it is a well-recognised phenomenon. The information available on the natural history of post-traumatic DI has been largely based on anecdotal experience and case reports. In their review of published case reports of post-traumatic hypopituitarism, Edwards and Clark (24), found DI to occur acutely in 23 of 53 cases, with later recovery in nine patients. In that review, cases were selected for inclusion on the basis that patients had some degree of anterior post-traumatic hypopituitarism, introducing a potential for bias, and it was unclear what methodologies were used to define acute or permanent DI.

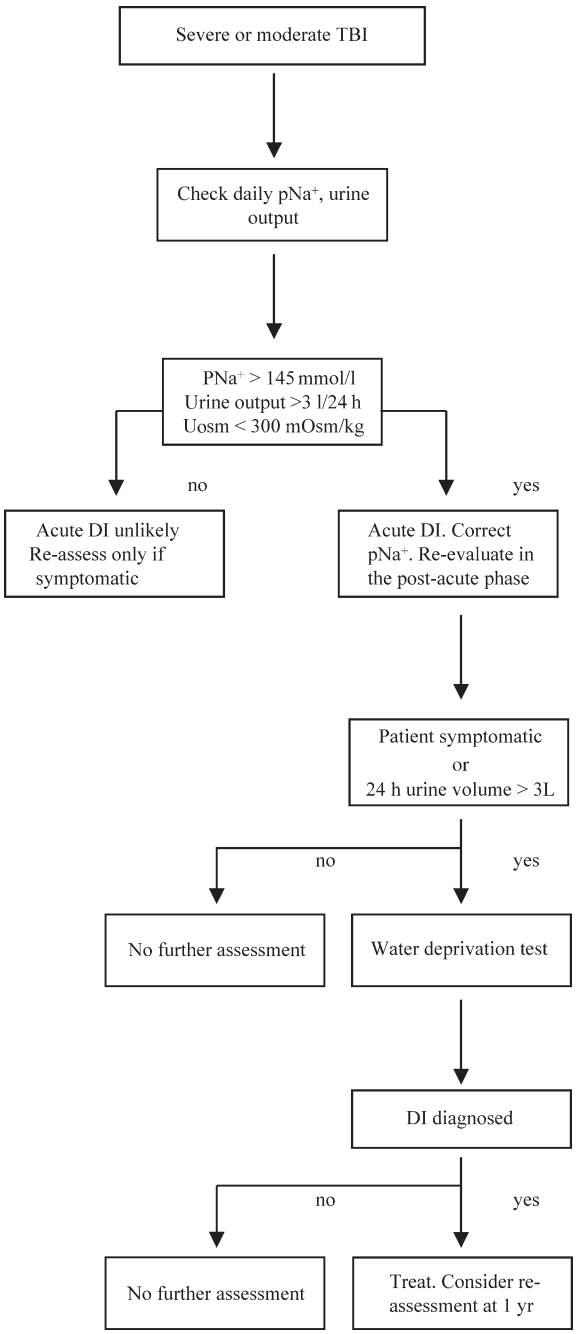

Figure 2 Suggested algorithm for the assessment of patients with DI after TBI. pNa^+, plasma sodium; Uosm, urine osmolality.

In this study, univariate analysis showed that acute post-traumatic DI was associated with lower GCS scores, although this association was only of borderline significance after logistic regression analysis, probably because of the colinearity between the GCS scores and the presence of cerebral oedema (another marker of TBI severity). However, since both variables are a measure of the severity of TBI, it is reasonable to conclude that acute DI is associated with more-severe injury. This is supported by the finding of a negative correlation between the GCS score and peak plasma osmolality and plasma sodium, and a positive correlation between the GCS score and peak urine osmolality, in the acute phase of TBI. The negative correlation between the GOS score (a measure of recovery) and peak acute phase plasma osmolality and plasma sodium suggests that plasma sodium has prognostic implications.

Post-traumatic DI may result from inflammatory oedema around the hypothalamus or posterior pituitary, with recovery as the swelling resolves. It can also result from direct damage to the paraventricular and supraoptic hypothalamic neurones, the pituitary stalk or axon terminals in the posterior pituitary. These abnormalities may be either transient, if the supraoptic and paraventricular neurones form new vascular connections, or become permanent if gliosis occurs (18).

Untreated DI leads to polyuria. In the early post-TBI period, water intake may be inadequate to compensate for the polyuria, because of impaired cognition, physical disability or coexistent hypodipsia. This can lead to hypernatraemic dehydration with increased morbidity and impairment of recovery. This is particularly a problem with adipsic DI Adipsic DI has been reported in association with TBI (25) and is associated with poor prognosis. However, none of the patients in our cohort had evidence of abnormal thirst appreciation when formally tested with the visual analogue scale.

Acute hyponatraemia secondary to SIADH was present in 14% of patients, with complete resolution in all cases. One patient had hyponatraemia secondary to post-traumatic ACTH deficiency, which emphasises the potentially serious impact of this complication of TBI. Studies on the prevalence of SIADH post-TBI have yielded conflicting data, with figs. ranging from as low as 2.3% to as high as 36.6% (26–30). The conflicting figs. in the literature reflect different selection criteria for the cohorts of patients studied, different criteria used to define SIADH, and varying duration of monitoring of plasma sodium concentrations following TBI.

Post-traumatic SIADH is caused by uncontrolled release of arginine vasopressin as a result of damage to the pituitary stalk or the posterior pituitary (31). Recognition and treatment of acute hyponatraemia is important as hyponatraemia in hospital patients is associated with increased morbidity and mortality (32, 33). It may have added importance in TBI patients because hyponatraemia increases the risk of cerebral oedema, which exacerbates the underlying brain injury, and increases the likelihood of seizures.

In conclusion, recognition of post-traumatic posterior pituitary dysfunction is important as abnormalities of water balance may increase morbidity following TBI. A suggested algorithm for the assessment and monitoring of post-traumatic DI is shown in Fig. 2. All patients presenting with features of DI following head trauma should be treated, and re-evaluated in the post-acute phase. Re-evaluation can be done by enquiry about symptoms of polyuria, nocturia and polydipsia, and measurement of 24 h urine volume (in patients receiving desmopressin therapy this should be stopped for 48 h prior to evaluation). In the presence of symptoms, or a 24-h urine volume greater than 3 l, then the patient should have a formal WDT Asymptomatic patients without elevated urine output are very unlikely to have persistent DI and further assessment is unnecessary. Similarly, asymptomatic patients without a history of acute post-traumatic DI do not require formal water-deprivation testing.

It is important to exclude glucocorticoid deficiency as a treatable and dangerous cause of acute hyponatraemia after TBI. SIADH should be corrected and monitored by serial measurements of plasma sodium, because of the risk of seizures and cerebral oedema. Because post-traumatic SIADH is transient, long-term follow-up is not necessary.

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