Disorders of water balance are well recognized after traumatic brain injury (TBI), but there are no reliable data on their true prevalence in post-TBI patients. We aimed to evaluate the prevalence of posterior pituitary dysfunction in a large cohort of survivors of TBI.

One hundred two consecutive patients (85 males) who suffered severe or moderate TBI were evaluated for diabetes insipidus (DI) at a median of 17 months (range 6–36 months) after the event, using the 8-h water deprivation test (WDT). Their results were compared against normative data obtained from 27 matched, healthy controls. Patients' medical records were retrospectively reviewed for the presence of abnormalities of salt and water balance in the immediate post-TBI period.

Twenty-two patients (21.6%) developed DI in the immediate post-TBI period (acute DI group), of whom five had abnormal WDT on later testing. In total, seven patients (6.9%) had abnormal WDT (permanent DI group), five of whom had partial DI.

Patients in the acute and permanent DI groups were more likely to have more severe TBI, compared with the rest of the cohort (P < 0.05). In the immediate post-TBI period, 13 patients (12.9%) had syndrome of inappropriate secretion of antidiuretic hormone, which persisted in one patient, and one other patient developed cerebral salt wasting.

Diabetes insipidus and syndrome of inappropriate secretion of antidiuretic hormone were common in the immediate post-TBI period. Permanent DI was present in 6.9% of patients who survived severe or moderate TBI, which is higher than traditionally thought. Identification of patients with partial posttraumatic DI is important because appropriate treatment may reduce morbidity and optimize the potential for recovery.

TRAUMATIC BRAIN INJURY (TBI) is the leading cause of death and disability in young adults (1, 2). Disorders of salt and water balance are the most commonly recognized medical complications in the immediate post-TBI period (3) and contribute to the early morbidity observed in TBI patients. Most cases of acute postranstraumatic diabetes insipidus (DI) are transient, and traditionally permanent DI after head trauma has been regarded as rare (4). However, patients with partial deficiency of arginine vasopressin (AVP) can be easily missed because they may have less severe symptoms and their posttraumatic clinical course is often complicated by significant neurological and cognitive disabilities.

Posterior pituitary function in survivors of TBI remains poorly investigated. There are no reliable data on the prevalence of permanent postranstraumatic DI. In this study, we assessed posterior pituitary function in a large cohort of patients after moderate or severe TBI.

**Patients and Methods**

**Patients**

One hundred two TBI patients (85 males), aged 15–65 yr (median, 28 yr; mean ± sd, 32.9 ± 14.7 yr) who were admitted to the neurosurgical unit in Beaumont Hospital between September 2000 and September 2002 and 27 matched healthy controls were included in the study (Table 1). Beaumont Hospital is the national neurosurgical center for the Republic of Ireland and has a catchment area of 3.5 million people. Patients were identified from the Beaumont Hospital head trauma database. The database contains demographic and mortality data and information about the nature and severity of the TBI but no information about any medical complications or drug therapy. Patients were eligible for inclusion in the study if they suffered severe or moderate TBI (see below), were between 15 and 65 yr of age, and were at least 6 months post the acute injury. Exclusion criteria were: pregnant women, patients with established renal disease, patients with raised creatinine (>120 μmol/liter), patients on lithium or other medications known to cause renal insensitivity to AVP, patients with diabetes mellitus with hemoglobin A1C greater than 6.5%, and patients with hypokalemia or hypercalcemia. One hundred twenty-eight patients were eligible for inclusion in the study. Twenty-six patients were excluded for the following reasons: four died since leaving the hospital, 13 left Ireland or were uncontactable, four were too ill to participate, and five declined to participate. Two of the participating patients, who were blindly selected from the database, were taking oral desmopressin treatment. They were discharged from the hospital on desmopressin following their TBI but were not previously investigated by means of the water deprivation test (WDT).

All patients had suffered severe or moderate head trauma according to the initial postresuscitation and preadmission Glasgow Coma Scale (GCS) score (Table 1) (5). Fifty-seven patients (55.9%) had documented severe head injury, as defined by a GCS score of 8/15 or less, and 42 (41.2%) had documented moderate injury, defined by a GCS score of 9/15 to13/15 (6). The three remaining patients had no documented GCS score but were admitted to the intensive care unit (ITU) and therefore were assumed to have a GCS score of 13 or less. The median GCS score was 8/15.

The causation of TBI was road traffic accidents in 44 patients, falls in 30 patients, alleged assault in 13 patients, and other mechanisms in 15 patients. Assessment of outcome post TBI was done using the Glasgow Outcome Scale score (7). All patients, except one, had computerized tomography (CT) evidence of brain injury (Table 1). CT appearance was...
classified as showing focal brain injury (extradural, subdural, or intracerebral hematomas) or diffuse brain injury (DBI; shearing axonal injury) (8). Eighty-six patients (84.3%) had focal brain injury and 15 patients (14.7%) had DBI. Seventy-two patients (70.6%) had CT evidence of raised ICP. Fifty-five patients (54%) underwent operative mass evacuation. Eighty-four patients (82.4%) had intracranial pressure monitoring and were sedated and ventilated in the neurosurgical ITU. The duration of ITU stay was 14 ± 10 d. Thirty-two patients (31.4%) had additional non-TBI trauma.

Methods

Patients were tested at a median of 17 months after injury (range 6–36 months). Testing was performed in the pituitary investigation day ward. Testing started at 0800 h. Undiluted blood samples were drawn from a heparinized cannula inserted in an antecubital vein.

The WDT (9) was carried out in all patients and controls. Fluids were allowed after this until 1600 h. The two patients on desmopressin were asked to withhold treatment on the evening before, and the morning of, the test.

Testing started at 0800 h. Plasma and urine osmolalities, urine volume, thirst score, blood pressure, and weight were measured at time 0800, 1000, 1200, 1400, and 1600 h. Plasma sodium was measured at 0800 and 1600 h. All studies were medically supervised, with the intention that studies would be stopped if subjects lost more than 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.

Patients' medical records were retrospectively reviewed for evidence of salt and water abnormalities in the acute post-TBI phase, defined as the time period from admission to the hospital until discharge to either a rehabilitation institute or home. All 102 patients had their anterior pituitary function assessed separately, and these results have been reported separately (10).

Definitions of abnormalities

WDT. The normal homeostatic response to dehydration is an increase in plasma osmolality (plasma sodium) and thirst appreciation. The increase in plasma osmolality, or more precisely in plasma sodium, triggers vasopressin release, which acts on the distal renal tubule to stimulate water resorption, resulting in reduced urine output and increased urine osmolality. However, in the presence of vasopressin deficiency or renal resistance to vasopressin action (i.e., DI), the renal concentrating ability is impaired and hypotonic polyuria results despite dehydration. This is the underlying rationale of using the WDT to diagnose DI.

In practice, however, there is no consensus regarding the exact definition of a normal response to water deprivation. Some authors define a normal response as a peak 8-h urine osmolality greater than 700 mOsm/kg (11), others use the 800 mOsm/kg cut-off (9), and others use a definition of peak urine to peak plasma osmolalities ratio of greater than 2 as normal (12).

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

In the immediate post-TBI period, DI was diagnosed if plasma sodium exceeded 145 mmol/liter in the presence of polyuria of more than 3.5 liter per 24 h and dilute urine (osmolality < 300 mOsm/kg) (13). Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was defined as: plasma osmolality less than 270 mOsm/kg, with a corresponding urine osmolality of greater than 100 mOsm/kg and a spot urine sodium more than 40 mmol/liter, in a euvoletic patient with normal glucocorticoid secretion and thyroid function (14). Cerebral salt wasting was defined as hypovolemic hyponatremia with diuresis and natriuresis, not explained by renal dysfunction or diuretics (15).

Statistical analysis

Prevalence figures are presented as percentages [95% confidence intervals (CIs)]. Continuous data [age, body mass index (BMI), water intake] were assessed for normality based on skewness and kurtosis and were also assessed for equality of variances between groups. As a result of these tests, the data were log transformed before testing for significance using the t test. However, for descriptive purposes, data are expressed as untransformed mean ± sd. GCS scores were analyzed using a Wilcoxon rank-sum test for nonparametric measurements, and categorical data were compared using the Fischer exact test. Multifactorial logistic regression models were developed to assess the effect of appropriate variables in the presence of other confounding variables on the development of DI and SIADH. The dependent variables for the models were acute DI, permanent DI, and acute SIADH; the independent variables were age, gender, BMI, GCS score, cerebral edema, operative mass evacuation, and basal skull fractures. Repeated measures ANOVA models were used to compare plasma and urine osmolalities, plasma sodium, urine volume, and thirst at different time intervals between groups. Multiple comparison tests, using a Bonferroni correction factor, were used to determine whether results reached significance.

The results were deemed significant for P < 0.05. Stata (version 8, Stata Corp., College Station, TX) was used for the statistical analysis.

Ethics

The study was approved by the ethics section of Beaumont Hospital Medical Research Committee. The purpose of the study was explained carefully to patients and relatives, who were provided with written information on the background to the study. After an interval of 1 wk, patients who agreed to participate signed written consent for inclusion in the study; written consent was given by next of kin, where appropriate.

Results

Posterior pituitary dysfunction in the immediate post-TBI period

In the acute post-TBI period, 22 patients (21.6%; 95% CI, 14.0–30.8%) had evidence of DI (acute DI group) (Table 2).
Univariate comparisons between the acute DI and the rest of patients are presented in Table 2. Multifactorial logistic regression analysis showed that acute DI was associated with a lower GCS score ($P = 0.043$) and the presence of cerebral edema ($P = 0.045$) but not related ($P > 0.05$) to age, gender, BMI, operative mass evacuations, DBI, or basal skull fractures. There was a negative correlation between the GCS score and the peak recorded plasma sodium ($r = -0.61, P = 0.01$).

Thirteen patients (12.7%; 95% CI, 7.0%–20.8%) had evidence of SIADH. None of the 13 patients was receiving medications known to cause the syndrome. The median plasma sodium was 128 mmol/liter (range 118–131 mmol/liter), and median blood urea was 4.3 mmol/liter (1.8–6.2 mmol/liter). The onset of SIADH was on d 1–2 in seven patients (54%), d 4–7 in five patients (38%), and one patient (8%) developed SIADH on d 18 post TBI. All 13 patients had normal glucocorticoid reserves and normal thyroid function. Multifactorial logistic regression analysis showed that SIADH was unrelated to age, BMI, gender, GCS score, the presence of cerebral edema, operative mass evacuation, or basal skull fracture ($P > 0.05$).

Hyponatremia due to cerebral salt wasting was diagnosed in one patient only, a 28-yr-old man who developed hyponatremia of 120 mmol/liter on d 8 post TBI associated with a lower GCS score ($P = 0.043$) and the presence of cerebral edema, operative mass evacuation, or basal skull fracture ($P > 0.05$).

**Posterior pituitary dysfunction in the chronic phase of TBI**

Seven patients (6.9%; 95% CI, 2.8–13.6%) had abnormal WDT (permanent DI group, Table 3), including both patients treated for DI with oral desmopressin. All seven patients had symptoms of polyuria, nocturia, and polydipsia. Five of these had unequivocal evidence of DI in the immediate post-TBI period; a sixth patient developed polyuria greater than 3 liters per 24 h on d 7 post TBI, although his plasma sodium remained normal, and the seventh patient had normal plasma sodium and urine output less than 2.5 per 24 h until discharge from hospital on d 17 post TBI. The other 17 patients with acute posttraumatic DI had normal WDT (transient DI group). The remaining 78 patients had normal WDT and no evidence of acute DI (non-DI group).

At the initiation of the WDT, patients with permanent DI had a significantly higher plasma osmolality (median 298, range 295–301 mOsm/kg) than healthy controls (median 287, range 284–291 mOsm/kg, $P < 0.001$). Figures 1 and 2 illustrate the changes in the measured variables during 8 h of water deprivation in the four groups. Repeated-measures ANOVA models showed that during 8 h water deprivation, patients with permanent DI had higher plasma and lower urine osmolalities, higher plasma sodium, higher urine volume, and higher thirst scores than patients in the transient DI, non-DI, or control groups ($P < 0.001$ for each variable, Figs. 1 and 2). All seven patients in the permanent DI group had normal thirst appreciation, and they consumed more water at the end of testing (1228 ± 276 ml) than patients in the non-DI group (563 ± 152 ml, $P < 0.001$), the transient DI group (581 ± 128 ml, $P < 0.001$), or healthy controls (590 ± 125 ml, $P < 0.001$). All measured variables were not significantly different between patients in the transient DI, non-DI, or control groups (Figs. 1 and 2).

Univariate comparisons between the permanent DI and non-DI groups are presented in Table 4. Multifactorial logistic regression analysis showed that permanent DI was associated with a lower GCS score ($P = 0.043$) but was not statistically related ($P > 0.05$) to age, BMI, gender, DBI, the presence of cerebral edema, operative mass evacuation, or basal skull fractures. There was no relationship between the presence of permanent DI and anterior pituitary dysfunction (data not shown).

Two patients had evidence of SIADH. One had persistent hyponatremia from the time of TBI, secondary to posttraumatic obstructive hydrocephalus, and the second patient had developed SIADH after the acute TBI, when the selective serotonin reuptake inhibitor citalopram was prescribed.

**Discussion**

We report the results of the largest study to date to examine the prevalence of posterior pituitary dysfunction in survivors of TBI. There have been very few reliable data in

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**TABLE 2.** Comparisons between patients with acute DI and rest of cohort

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Acute DI (n = 22)</th>
<th>Acute non-DI (n = 80)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>M: F ratio</td>
<td>28.8±11.9</td>
<td>34.1±15.3</td>
<td>0.153</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.2±5.4</td>
<td>24.5±3.7</td>
<td>0.552</td>
</tr>
<tr>
<td>GCS score</td>
<td>6 (5-7)</td>
<td>8 (6-12)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cerebral edema, n (%)</td>
<td>20 (91)</td>
<td>52 (65)</td>
<td>0.018</td>
</tr>
<tr>
<td>Mass evacuation, n (%)</td>
<td>11 (50)</td>
<td>44 (55)</td>
<td>0.810</td>
</tr>
<tr>
<td>Basal skull fracture, n (%)</td>
<td>4 (18)</td>
<td>12 (15)</td>
<td>0.744</td>
</tr>
</tbody>
</table>

M, Male; F, female.

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**TABLE 3.** Characteristics of the seven patients with permanent DI from a cohort of 102 with TBI

<table>
<thead>
<tr>
<th>Subject/gender</th>
<th>Age (yr)</th>
<th>Cause of TBI</th>
<th>GCS score</th>
<th>Basal skull fracture</th>
<th>Acute DI</th>
<th>Peak Posm (mOsm/kg)</th>
<th>Peak Uosm (mOsm/kg)</th>
<th>Anterior pituitary status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M</td>
<td>19</td>
<td>RTA</td>
<td>5</td>
<td>N</td>
<td>Y</td>
<td>311</td>
<td>165</td>
<td>Normal</td>
</tr>
<tr>
<td>2/M</td>
<td>25</td>
<td>RTA</td>
<td>13</td>
<td>N</td>
<td>Y</td>
<td>305</td>
<td>520</td>
<td>GTD</td>
</tr>
<tr>
<td>3/M</td>
<td>52</td>
<td>RTA</td>
<td>7</td>
<td>Y</td>
<td>N</td>
<td>305</td>
<td>467</td>
<td>Normal</td>
</tr>
<tr>
<td>4/M</td>
<td>25</td>
<td>RTA</td>
<td>3</td>
<td>N</td>
<td>Y</td>
<td>314</td>
<td>80</td>
<td>Normal</td>
</tr>
<tr>
<td>5/F</td>
<td>32</td>
<td>Assault</td>
<td>5</td>
<td>N</td>
<td>Y</td>
<td>308</td>
<td>480</td>
<td>GHD, ACTHD</td>
</tr>
<tr>
<td>6/M</td>
<td>21</td>
<td>RTA</td>
<td>6</td>
<td>N</td>
<td>Y</td>
<td>307</td>
<td>506</td>
<td>Normal</td>
</tr>
<tr>
<td>7/M</td>
<td>24</td>
<td>Fall</td>
<td>4</td>
<td>N</td>
<td>N</td>
<td>304</td>
<td>521</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Posm, Plasma osmolality; Uosm, urine osmolality; RTA, road traffic accident; Y, yes; N, no; GHD, GH deficiency; GTD, gonadotropin deficiency; ACTHD, ACTH deficiency; M, male; F, female.
the literature concerning the prevalence of posttraumatic DI. Our data show that frequency of permanent posttraumatic DI is higher than previously thought (4). This can be explained by our finding that five of the seven DI patients had partial defects, with mild symptoms, which had been clinically overlooked and gone undiagnosed.

Bohlen et al. (18) studied 38 patients, 5 wk after mild TBI. They reported that eight (21%) had evidence of mild DI, a much higher figure than in our cohort. However, the authors measured early-morning plasma and urine osmolalities after an unobserved overnight fast, a method that has been shown to be inaccurate for the diagnosis of DI (19). Furthermore, they defined DI on the basis of a plasma osmolality greater than 295 and urine osmolality less than 1000 mOsm/kg.
cut-offs that are too liberal and likely to result in overdiagnosis. In their review of published case report of posttraumatic hypopituitarism, Edwards and Clark (20) found DI to occur in 23 of 53 case reports, with transient symptoms in nine patients, although cases were selected for inclusion on the basis that patients had hypopituitarism, introducing a potential for bias. Our prevalence of DI is higher than that reported in a retrospective study, Wong et al. (21), who found DI in 3.7% of neurosurgical intensive care patients, although they did not report on the frequency of DI in the subgroup of TBI patients. We feel that our data, derived from a large, unselected cohort studied with standard methodologies, are more likely to reflect the true prevalence of persistent DI after TBI.

The prevalence of acute posttraumatic DI in this study was similar to that reported in a recent smaller prospective study of 50 patients studied at the time of acute TBI (22). However, in contrast to the last study, we found a significant association between acute posttraumatic DI and more severe TBI, as indicated by lower GCS scores or CT evidence of raised ICP due to cerebral edema. Naturally, patients with cerebral edema tend to have lower GCS scores; therefore, the inherent association between the two variables makes it more difficult to statistically separate their independent effects on the development of acute DI. However, because both variables are markers of the severity of TBI, our conclusion that acute DI is associated with more severe trauma remains valid. This conclusion is further supported by the finding of a negative correlation between the GCS score and the peak recorded plasma sodium, which is a surrogate marker for the severity of DI. The findings in this study concur with anecdotal reports and clinical experience and may reflect the larger number of patients in our current study, which allowed more valid statistical comparisons.

Five of the 22 acute DI patients were found to have persistent (permanent) DI, whereas the remaining 17 had no evidence of any abnormalities in any of the variables measured, indicating complete recovery of posterior pituitary function. Interestingly, two of the seven patients with permanent DI had no definite acute abnormalities. It is possible that their partial DI was masked by adequate hydration with iv fluids or drinking in the acute post-TBI period. Alternatively, DI may have developed in the postacute phase, which has been previously reported (23). Two of the seven patients with permanent DI had been on desmopressin therapy before the commencement of the study. However, the investigators were unaware of this fact, and the two patients were not preselected. Both patients had severe DI with good clinical response to desmopressin. The other five patients had milder symptoms and were considered to have partial AVP deficiency (12), which has previously been reported after TBI (24). Although the criteria that we used to define DI using the WDT may also be met by some subjects with primary polydipsia, the finding of high plasma osmolalities, both at the initiation and the conclusion of the WDT in all patients with abnormal WDT, confirms the diagnosis of DI.

Patients who developed permanent DI were more likely to have lower GCS scores, indicating more severe injury. In contrast to data from the immediate post-TBI period, there was no relationship between the presence of cerebral edema and the development of permanent DI. Such an association cannot be excluded because the small number of subjects in the permanent DI group may have precluded reliable statistical comparisons. Another possible explanation is that transient DI may be related, in some cases, to edema around the hypothalamic-pituitary region, which later resolves, with resumption of normal physiological AVP secretion. In contrast, permanent DI may result from direct irreversible damage to the hypothalamic paraventricular and supraoptic neurons or their projection to the posterior pituitary.

Twenty-eight percent of this cohort had evidence of one or more of anterior pituitary hormone deficiency; however, we found no association between anterior hypopituitarism and acute or chronic posterior pituitary dysfunction.

In this study, we did not measure plasma vasopressin levels. Plasma vasopressin level can be useful in differentiating patients with cranial DI from those with nephrogenic DI (25). However, we were careful to exclude any patients with medical conditions or medications known to cause nephrogenic DI. In addition, five of the seven patients with permanent DI had clear evidence of DI presenting acutely in the immediate post-TBI period, and all seven patients responded clinically to treatment with desmopressin, with concentration of urine to more than 700 mOsm/kg. We are confident that all seven patients with DI had vasopressin deficiency; and because the 95 patients classified as normal had unequivocally normal WDT, with all measured variables similar to healthy controls, it is highly unlikely that AVP measurement would have altered the diagnosis in any individual studied.

Posttraumatic DI may result from inflammatory edema around the hypothalamus or posterior pituitary, with resolution as the swelling resolves. It can also result from direct damage to the paraventricular and supraoptic hypothalamic neurons, the pituitary stalk, or axon terminals in the posterior pituitary. These abnormalities can be transient if the supraoptic and paraventricular neurons form new vascular connections or become permanent (4).

Posttraumatic SIADH is caused by uncontrolled release of AVP as a result of damage to the pituitary stalk or the posterior pituitary (26). Acute hyponatremia secondary to SIADH was present in 12.7% of patients. Studies on the prevalence of SIADH post-TBI have yielded conflicting data, with figures ranging from 2.3 to 36.6% (22, 27–31). The conflicting figures in the literature may reflect different selection criteria for the cohorts of patients studied, different criteria used to define SIADH, and varying duration of monitoring after TBI. SIADH persisted in only one patient, who had obstructive hydrocephalus. Glucocorticoid deficiency was excluded by dynamic tests of the hypothalamic-pituitary-adrenal axis in all cases. We are therefore confident that none of the patients with SIADH in this cohort had undiagnosed glucocorticoid deficiency. Cerebral salt-wasting syndrome is a rare complication of head trauma, which has been reported previously (15), but we were able to diagnose with confidence in only one patient.

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 dehydration and
a hyperosmolar state with impairment of rehabilitation and increased morbidity. This is particularly a problem with adipsic diabetes insipidus; thirst appreciation is almost uniformly normal in DI (32), but adipsic DI has been reported in association with TBI (33) and is associated with poor prognosis.

In conclusion, we have shown, in a large cohort of survivors of TBI, a significant frequency of early and late posterior pituitary dysfunction. Recognition of these treatable abnormalities is important, to maximize the potential for recovery, in this high morbidity group of patients. Therefore, all patients presenting with acute posttraumatic DI should be re-evaluated in the postacute phase using the WDT. Patients without a recognized history of acute posttraumatic TBI and who have no symptoms of thirst, polyuria, or nocturia and a 24-h urine output of less than 3 liters need no further assessment. However, in the presence of symptoms or polyuria of more than 3 liters/d, a WDT should be performed.

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