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Diabetes Insipidus and Traumatic Brain Injury

Yi-Chun Chou, Tzu-Yuan Wang and Li-Wei Chou
*China Medical University Hospital,
Department of Physical Medicine and Rehabilitation
Taiwan, R.O.C.*

1. Introduction

Traumatic brain injury (TBI) is a leading cause of mortality and morbidity worldwide and is the major cause of disability among children and young adults in the United States (1999; Adekoya, Thurman et al. 2002). Recent data show that there are over a million emergency room visits for TBI in the United States annually. The majority of such emergency room visits are for patients with mild TBI, defined as a post-resuscitation Glasgow Coma Scale with a score of 13–15 (Teasdale and Jennett 1974). However, approximately 300,000 TBI victims are hospitalized annually. Of these, over 50,000 die and over half of the survivors have permanent neurobehavioral and quality of life problems, the most common being memory and concentration deficits, depression, anxiety, fatigue, and loss of emotional well-being (Levin, Gary et al. 1990; Kraus and McArthur 1996; Hellowell, Taylor et al. 1999; Kelly, McArthur et al. 2006; Rutland-Brown, Langlois et al. 2006).

Diabetes insipidus (DI) from post-TBI hypopituitarism was first reported in 1921 (Rouvillois, Reverchon et al. 1921) and, in the 1970s, multiple case reports were published, documenting posterior pituitary dysfunction (Massol, Humbert et al. 1987; Halimi, Sigal et al. 1988). DI may be of a central (neurogenic), nephrogenic, gestational, dipsogenic, adipsic, or psychogenic type. The most common DI, the central type, which follows brain injury or surgery to the region of the pituitary and hypothalamus, is noted in previous literature review. DI is characterized by a diminished secretion of antidiuretic hormone, also known as arginine vasopressin (AVP). Neuroendocrine abnormalities following brain injury may occur with a much higher prevalence than previously realized, and represent an underdiagnosed consequence of brain injury.

The prevalence of central DI among all kinds of neuroendocrine derangements after TBI in acute to chronic phases was 1.7%-26%. The development of DI seems to correlate with the severity of trauma in spite of more cases of permanent DI being reported in mild TBI cases. Central DI caused by brain injury is detectable because of polyuria and polydipsia in patients, but the occasions of DI are almost transient, leading to ignorance of its precise diagnosis and adequate treatment.

In this chapter, diabetes insipidus was considered as central diabetes insipidus, which is a result of TBI.

2. Epidemiology of diabetes insipidus after traumatic brain injury

TBI involves, not only the primary mechanical event, but also secondary implications, such as pituitary insufficiency. Large neuropathological studies, including a total of 638 cases,

established a large frequency of 26.4% to 86% hypothalamic-pituitary damage in patients who died as a consequence of head injury (Ceballos 1966; Kornblum and Fisher 1969; Crompton 1971; Pierucci, Gherson et al. 1971; Harper, Doyle et al. 1986; Salehi, Kovacs et al. 2007). Schneider et al. (Schneider, Kreitschmann-Andermahr et al. 2007) conducted 19 studies, which included 1137 patients, and pointed out that the pooled prevalence of hypopituitarism in the chronic phase after TBI was 27.5% (95% confidence interval [CI], 22.8%-28.9%). The prevalence of DI ranged 1.7% to 26% among all kinds of neuroendocrine derangements after brain injury in acute to chronic phases (Klose, Juul et al. 2007; Behan, Phillips et al. 2008). In a prospective cross-sectional and longitudinal study on posterior pituitary function after TBI, the prevalence of DI, diagnosed using the water deprivation test criterion standard, was 26% in the acute phase (Agha, Sherlock et al. 2005) and 6.9% among long-term survivors (Agha, Thornton et al. 2004).

Literature regarding adults diagnosed with DI following TBI have flourished since 1998, and the findings of key studies are summarized in Table 1. Some observations are supported by a series of recent findings reported by Agha et al. In the study of 102 TBI survivors assessed at a median of 17 months following moderate to severe injury, acute DI and permanent DI were detected in 21.6% and 6.9% of patients, respectively. In 2003, Agha and colleagues also discovered a high frequency of DI (26%) in survivors (n=50) of moderate to severe TBI (range of 7-12 days).

Study period	Author, year	Number	Population	Onset Time of DI after TBI	Severity of TBI (GCS)	Prevalence of DI
-	Boughey et al, 2004 (Boughey, Yost et al. 2004)	888	USA	176 days	<6	2.9%
1998-2002	Alfonso Leal-Cerro, 2005 (Leal-Cerro, Flores et al. 2005)	170	Male: 88% Mean age 28 years Spain	Episode of TBI	<8: 100%	1.7%
2000-2002	Agha et al, 2004 (Agha, Thornton et al. 2004)	102	Males:83% 15-65 years Ireland	range 6-36 months, Median 17 months	9-12: 44% <9: 56%	Acute DI: 21.6% Permanent DI: 6.9%
2003	Agha et al, 2004 (Agha, Rogers et al. 2004)	50	Male: 76 %,Age:- Ireland	12 days (range 7-20)	9-12: 36% <9: 64%	26%
2003-2005	Klose et al, 2007 (Klose, Juul et al. 2007)	104	Male: 75% median age 41 (range 18-64) years Denmark	13 (10-27) months postinjury	13-15: 42% 9-12: 19% <9: 38%	2%
2003	Aimaretti et al, 2004 (Aimaretti, Ambrosio et al. 2004)	100	Male 69% age 37.1±1.8 years Italian	3 months	13-15: 55% 9-12: 24% <9: 21%	4%

Table 1. Prevalence of diabetes insipidus after traumatic brain injury across countries

2.1 Mechanism of diabetes insipidus after traumatic brain injury

DI is characterized by a diminished release of AVP, resulting in variable degrees of hypotonic polyuria. Paucity of AVP may be caused by disorders that act at one or more of the sites involved in AVP secretion, namely, the hypothalamic osmoreceptors; the supraoptic or paraventricular nuclei; or the superior portion of the supraopticohypophyseal tract (Rose, Narins et al. 2001) (Fig. 1). Autopsy results have demonstrated different types of lesions, from damage to the pituitary capsule (the most frequent form of pituitary damage after TBI, occurring in 23.3%-59% of patients) to injury to the anterior and the posterior lobes and the pituitary stalk, in the form of hemorrhage, necrosis, and fibrosis (Ceballos 1966; Kornblum and Fisher 1969; Crompton 1971; Pierucci, Gherson et al. 1971; Harper, Doyle et al. 1986; Salehi, Kovacs et al. 2007). In contrast, damage to the tract below the median eminence or to the posterior pituitary generally induces only transient polyuria because AVP produced in the hypothalamus can still be secreted into the systemic circulation via the portal capillaries in the median eminence (Rose, Narins et al. 2001). Therefore, the severity of injury is unlikely to be the cause of hypopituitarism that would more likely be determined as trauma characteristics and/or unknown vascular mechanisms (Aimaretti, Ambrosio et al. 2004). There has ever been a report, showing that DI occurred secondary to penetrating spinal cord trauma (Kuzeyli, Cakir et al. 2001).

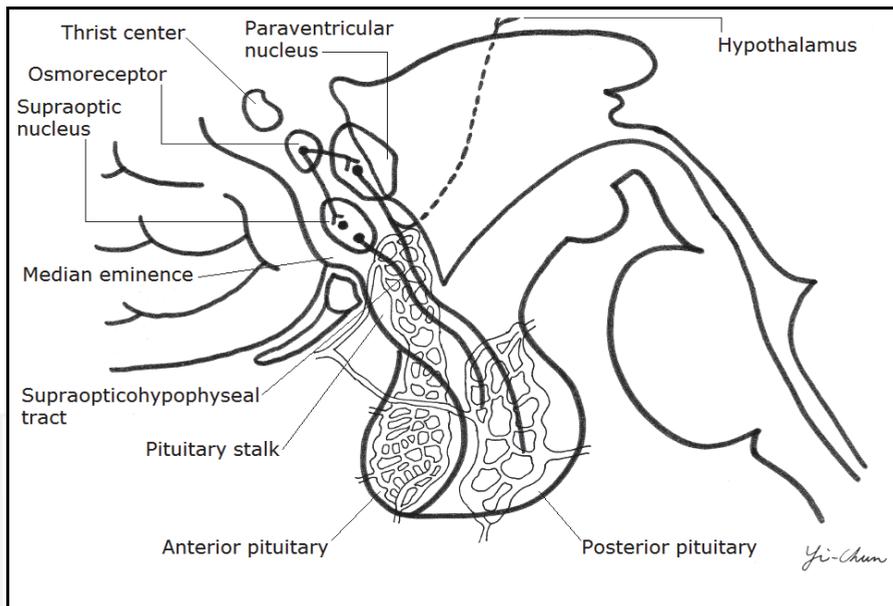


Fig. 1. Arginine vasopressin is transported from the hypothalamus through the neural component of the pituitary stalk and stored in nerve terminals in the posterior pituitary.

2.1.1 Imaging studies of the hypothalamic-pituitary region after traumatic brain injury

The posterior pituitary is known to be hyperintense on sagittal T1-weighted magnetic resonance imaging (MRI) of normal subjects. The absence of this finding serves as a nonspecific indicator of DI, although the frequency of hyperintensity declines with aging in

normal subjects (Brooks, el Gammal et al. 1989). The frequency of these radiologic abnormalities in patients with DI is poorly defined. Maghnie et al. (Maghnie, Cosi et al. 2000) investigated the clinical presentation, the morphologic characteristics of the pituitary region on MRI, and the size of the pituitary stalk over time in patients who had DI from a variety of causes. The initial radiological findings, based on Marshall Classification, and/or the presence of cranial fractures did not predict the development of hypopituitarism (Bondanelli, De Marinis et al. 2004).

With regard to the anatomical integrity of the hypothalamic-pituitary region, autopsy series from patients with fatal TBI displayed different degrees of damage to this region (Kornblum and Fisher 1969; Lieberman, Oberoi et al. 2001). This further supports the hypothesis that TBI severity is an important risk factor in the development of hypopituitarism. However, in the study made by Bondanelli et al. (Bondanelli, De Marinis et al. 2004), a significant number of patients with minimal TBI exhibited some degree of hypopituitarism. Also, in the Bondanelli study, the occurrence of anatomical lesions on MRI was low in patients with severe TBI and hypopituitarism. This was also seen in the series of studies made by Cytowic et al. (Cytowic, Smith et al. 1986). Therefore, in patients without radiological alteration, the functional damage to the hypothalamic-pituitary region may be due to a secondary hypoxic insult. Another possibility is diffused axonal injury caused by the acceleration-deceleration along rotational forces in motor vehicle crashes. Diffused axonal injury is the principal pathology in 40 to 50 percent of TBI hospital admissions, and is the predominant cause of loss of consciousness. Secondary to shearing injury, diffused axonal injury is seen in the midline structures. Most often, the initial CT and MRI scans have no specific findings and, therefore, it is only conclusively diagnosed microscopically (Cytowic, Smith et al. 1986). This explains why some patients with TBI, who undergo radiological scans, do not display any specific findings.

However, recent MRI studies of the pituitary demonstrated pathological changes consistent with vascular injury. In the acute phase, the pituitary glands of TBI patients are significantly enlarged as compared with normal healthy control subjects. Many also demonstrate other abnormalities, such as hemorrhage, infarction, signal abnormalities, and/or partial stalk transection (Maiya, Newcombe et al. 2008). In the chronic phase, patients often demonstrate pituitary volume loss or empty sella, followed by abnormal pituitary gland signal heterogeneity, perfusion deficits, and/or lack of posterior pituitary signal (Schneider, Samann et al. 2007). The recently published study of 70 TBI patients with long-term follow-up suggests that the degree of brain injury, as defined by acute CT (presence of diffused brain swelling and evacuated intracerebral hematoma or multiple contusions, in particular), is the strongest predictor of subsequent hypopituitarism (Bavisetty, McArthur et al. 2008).

2.2 Differential diagnosis of diabetes insipidus following traumatic brain injury after neurosurgery

Polyuria can be defined as a urine output exceeding 3 L/24 h in adults and 2 L/m² in children. It must be differentiated from the more common complaints of frequency or nocturia, which are not associated with an increase in the total urine output. Differential diagnosis has to be kept in mind when TBI patients undergoing neurosurgery have huge amounts of urine output because most cases of polyuria, at this time, are not caused by DI (Seckl and Dunger 1989). The more common causes are excretion of excess fluid administered during surgery and an osmotic diuresis, resulting from treatment aimed at minimizing cerebral edema using mannitol or glucocorticoids (Bohn, Davids et al. 2005).

The diagnosis of DI following TBI in the immediate postoperative period may be more difficult because polyuria can occur during this period, secondary to a variety of causes. When polyuria begins, establish whether it is secondary to water or solute excretion. A solute diuresis may be a result of hyperglycemia; inability to retain sodium, secondary to corticosteroid deficiency; high urea levels; or the residual effect of osmotic diuretics so commonly used in neurosurgical procedures. When the diuresis is secondary to solute excretion, the urinary specific gravity is usually between 1.009 and 1.035; the urine osmolality is usually between 250 and 320 mOsm/kg; the serum sodium is normal or slightly decreased; and thirst is not usually a complaint. When the diuresis is secondary to water excretion, the urinary specific gravity is usually between 1.001 and 1.005; the urine osmolality is between 50 and 150 mOsm/kg; the serum sodium is usually normal or increased; and thirst is usually a prominent feature. The latter picture is, of course, what is seen in diabetes insipidus. When it is determined that the diuresis is secondary to the excretion of a water load, the differential diagnosis includes the following:

1. Diabetes insipidus.
2. Chronic renal insufficiency. Renal function tests are abnormal and the patient is usually azotemic.
3. Multiple myeloma, amyloidosis, sickle cell disease, and a peculiar phenomenon sometimes seen after relief of obstructive uropathy are rarer causes of an inability to concentrate urine. These problems usually cause little difficulty in the differential diagnosis.
4. Recovery phase of acute tubular necrosis. The clinical sequence of events in this problem usually makes the diagnosis clear.
5. Fluid overload. Careful attention must be paid to fluid administration during the intraoperative and the immediate postoperative periods when the patient may receive excessive amounts of parenteral fluids. If these fluids are electrolyte-free and do not cause a solute diuresis, the patient may retain excessive quantities of water. As the patient excretes this excessive water load, he may have an output which exceeds his intake. These conditions can be differentiated from DI by measuring urine osmolality, the response to water restriction, and the administration of AVP.

You may conclude that a patient has DI if either

1. The plasma sodium exceeds 150 mmol/l in the presence of polyuria of $> 3 \text{ L} / 24 \text{ h}$ in an acute clinical setting; or
2. Following an overnight water deprivation test or an 8-h observed water deprivation test, urine osmolality is less than 600 mOsmol/kg; or
3. Considering a hypertonic saline water infusion test with measuring plasma AVP level while water deprivation test as a great burden to patients;
4. If these do not occur, responsiveness of the renal tubule should be demonstrated by vasopressin administration.

Once DI after TBI is adequately evaluated and accurately measured, the replacement of AVP may be considered.

3. Outcome and association factors of diabetes insipidus after traumatic brain injury

Admittedly, the pathophysiology of TBI is complex and is still poorly understood in many ways because there is a wide spectrum of injury severity, injury mechanisms, and brain

injury patterns across all age ranges. In spite of more cases of permanent DI being reported in mild head injury cases (Segal-Lieberman, Karasik et al. 2000; Chou, Wang et al. 2009), the development of DI seems to correlate with the severity of trauma (Tsagarakis, Tzanela et al. 2005). The pooled prevalence of hypopituitarism is greater in patients with severe TBI compared with those with mild or moderate TBI (Klose, Juul et al. 2007; Salehi, Kovacs et al. 2007; Hadjizacharia, Beale et al. 2008). Recent prospective data suggest that the incidence of DI may be as high as 26% in the acute phase immediately following TBI, although up to 70% of cases fully recover from DI within 12 months (Agha, Sherlock et al. 2005). The incidence of acute DI in severe TBI is high, especially in penetrating injuries (Hadjizacharia, Beale et al. 2008). Independent risk factors for DI include a Glasgow Coma Scale lower or equal to 8, cerebral edema, and a head Abbreviated Injury Score higher than 3 (Hadjizacharia, Beale et al. 2008). The risk of pituitary insufficiency increases in patients with severe TBI as opposed to those with mild TBI [odds ratio (OR) 10.1, 95% confidence interval (CI) 2.1-48.4, $P = 0.004$], and in those patients with increased intracerebral pressure (OR 6.5, 95% CI 1.0-42.2, $P = 0.03$) (Klose, Juul et al. 2007). Posttraumatic DI was not associated with the presence of anterior hypopituitarism but was associated with more severe head trauma and the presence of cerebral edema on CT scan (Agha, Thornton et al. 2004). Moreover, severe TBI associated with basilar skull fracture, hypothalamic edema, prolonged unresponsiveness, hyponatremia, and/or hypotension is associated with a higher occurrence of endocrinopathy (Powner, Boccalandro et al. 2006).

By contrast, Agha et al. reported in 2003 that the occurrence of post-trauma DI is unrelated to the severity of TBI, as assessed by the Glasgow Coma Scale score. Lieberman et al. (Lieberman, Oberoi et al. 2001) also found no correlation between severity of head injury and pituitary dysfunction. Trauma severity was not uniformly identified as predictive of post-traumatic DI, which may be explained by a variety of reasons. The choice of diagnostic criteria, timing after TBI, identification of TBI severity, and thus of tests and cut-off limits, as well as that of inclusion and exclusion criteria, are of paramount importance in prevalence studies and the identification of predictors. For example, DI has been reported to occur in 13% of patients in the late head injury period, with diagnosis made on the basis of random plasma and urine osmolalities, which are insufficiently accurate for either clinical or research purposes (Bohnen, Twijnstra et al. 1993). Also, alcohol and drug intoxication are serious confounders of the initial GCS scoring. Not all studies exclude patients with chronic alcohol or drug abuse and, as a result, this obvious confounder may have contributed to the observed inequalities.

DI from post-traumatic hypopituitarism had been documented as a potential contributor to morbidity and, possibly, mortality. Boughey et al. (Boughey, Yost et al. 2004) reported that patients who develop DI early (in the first 3 days) have a higher mortality rate than those who develop DI later. The mean onset time of DI in nonsurvivors (1.5+-0.7 days) is shorter compared with survivors (8.9+-10.2 days) ($P < 0.001$). The development of DI after TBI carries a 69% mortality rate, and if the onset is within the first 3 days after injury, the mortality rate rises to 86%.

3.1 Transient or persistent diabetes insipidus

Actually, destruction of the hypothalamic centers or division of the supraoptic tract above the median eminence causes permanent DI. Transection below the median eminence, even removal of the posterior pituitary lobe, produces only a transient polyuria. However, DI, following brain injury or surgery in the hypothalamic-pituitary area, can follow a variety of

patterns in its development. Early prognostication as regards the permanence of DI should not be made because of a marked variation in the eventual outcome. Cerebral edema generally appears within 12 to 24 hours and is most marked at 48 to 72 hours. This edema may functionally impair cells which are structurally intact. A temporary DI can develop and is subsequently resolved as the edema clears. There are varying degrees of chronic antidiuretic hormone deficiency, with the urinary output being related to the number of viable cells.

These initial insults, as well as transient events and treatments during the early injury phase, can evidently impact hypothalamic-pituitary function both acutely and chronically after injury. In most occasions, DI is transient, but persisting DI may develop with an incidence of 6.9%-7.5% among TBI victims (Tsagarakis, Tzanela et al. 2005). Severe damage to the hypothalamus or the supraopticohypophyseal tract by neurosurgery or trauma often results in a typical triphasic response (Rose, Narins et al. 2001; Ghirardello, Hopper et al. 2006) (Fig. 2). There is an initial polyuric phase, beginning within 24 hours and lasting 4 to 5 days. This phase reflects the inhibition of AVP release because of hypothalamic dysfunction (Seckl and Dunger 1989). This is followed, on days 6 to 11, by an antidiuretic phase, in which stored hormone is slowly released from the degenerating posterior pituitary. During this stage, excessive water intake can lead to hyponatremia in a manner similar to that in the syndrome of inappropriate AVP secretion. Permanent DI may then ensue after the posterior pituitary stores are depleted.

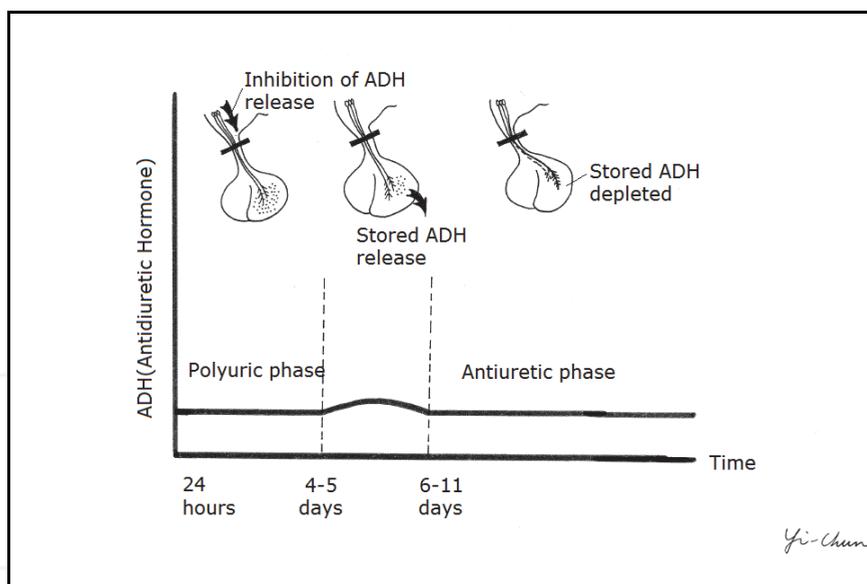


Fig. 2. Tri-phases of central diabetes insipidus after severe damage to the hypothalamus or supraopticohypophyseal tract

There was rarely any statement or discussion associated with the factors implicated in the persistence and the duration of post-trauma DI. Although one study has discovered that postoperative hypernatremia (higher than 145 mmol/L) within the first five days has a high predictor value for permanent DI development (Sigounas, Sharpless et al. 2008). Different

phases of post-head injury were presented with various amounts of urine output clinically. Post-traumatic DI is often transient, and suggests that patients need to be followed up to determine the true prevalence of late DI following TBI (Edwards and Clark 1986).

4. Management of diabetes insipidus after traumatic brain injury

The probability of developing hypopituitarism is based on the severity of the TBI. However, discrepancies in recent studies indicate that minimal TBI can also result in hypopituitarism. Thus, patients with moderate to severe TBI must be screened, and those with minimal TBI must be monitored for hypopituitarism. Alterations in pituitary hormones may develop subtly or generate clinical manifestations similar to those attributed to head trauma. Therefore, pituitary dysfunction may be overlooked or viewed as a result of postconcussional causes and escape diagnosis (Edwards and Clark 1986; Benvenga, Campenni et al. 2000). The modern therapeutic paradigm for moderate and severe TBI victims is centered on the concepts of rapidly treating the primary brain injury, correcting or avoiding secondary brain insults, and optimizing cerebral blood flow and metabolism (Edwards and Clark 1986; Benvenga, Campenni et al. 2000; Kelly, Gonzalo et al. 2000; Agha, Rogers et al. 2004; Dimopoulou, Tsagarakis et al. 2004). The temporal relationship between TBI and the occurrence of hypopituitarism is observed in three phases, namely, acute, recovery, and chronic. Agha et al. examined the prevalence of anterior and posterior pituitary dysfunctions in the acute (7–21 days) phase following TBI, and those series-identified deficiencies in need of immediate replacement, such as ACTH deficiency and posterior pituitary dysfunction (Agha, Rogers et al. 2004).

Adequate secretion of AVP is crucial in water homeostasis. Inadequate AVP secretion leads to varying degrees of water loss. Water intake may be inadequate to compensate for the water loss because of impaired cognition, physical disability, or coexistent hypodipsia that may occur in the early post-TBI period. This may lead to hypernatraemic dehydration with increased morbidity and impairment of recovery (Maggiore, Picetti et al. 2009). Therefore, daily sodium measurements and fluid charts are indicated in all TBI patients during the early post-injury period. Therapeutic intervention with desmopressin is indicated in patients with severe forms of this disorder. Caution is required for the occasional development of the syndrome involving inappropriate AVP release that may also occur as a result of brain trauma, and increase the likelihood of seizures. If polyuria persists during the late-phase of TBI, a persistent DI should be appropriately diagnosed and treated.

4.1 Drugs for diabetes insipidus after traumatic brain injury

Considering that the primary problem in DI is the deficient secretion of AVP, control of the polyuria can be achieved by hormone replacement. In the past, intramuscular injections of vasopressin (Pitressin) tannate in oil was used to control, which is no longer available. This preparation had two problems, namely, the requirement of intramuscular administration and the occasional development of antivasopressin antibodies, with a secondary increase in urine output that appear AVP resistant (Vokes, Gaskill et al. 1988). Pitressin has many side effects of anaphylaxis (cardiac arrest and/or shock), circumoral pallor, arrhythmias, decreased cardiac output, angina, myocardial ischemia, peripheral vasoconstriction, gangrene, abdominal cramps, nausea, vomiting, passage of gas, tremor, vertigo, pounding in head, bronchial constriction, sweating, urticaris, cutaneous gangrene et al. Otherwise, pitressin has two actions with V1 and V2 receptors. As DI is caused by decreased V2

receptor function owing to paucity of AVP secretion, it is better to have V2 receptor action alone without V1 receptor action as drug. Consequently, using DDAVP (desmopressin acetate) instead of Pitressin is better. Desmopressin comes in liquid form. That is, it is usually administered intranasally and in an oral tablet form. The usual daily maintenance dose is 10 to 20 μg once or twice a day.

An oral tablet preparation of desmopressin is also available (Stenberg and Lackgren 1994). The absorption of desmopressin in normal persons is decreased by 40 to 50 percent when taken with meals (Rittig, Jensen et al. 1998). The oral form has about one-tenth to one-twentieth the potency of the nasal form because only about five percent is absorbed from the gut. Thus, a 0.1 mg tablet is the equivalent of 2.5 to 5 μg of the nasal spray. Although patients generally prefer the oral preparation because of ease of administration, not all patients have an adequate response. As a result, we recommend starting with the intranasal preparation. This ensures that the patient understands what constitutes a good antidiuretic response prior to performing a trial of oral therapy. If DDAVP cannot be administered intranasally or orally, it can be given subcutaneously. A usual antidiuretic dose is 1 μg , administered subcutaneously every 12 hours. Alternatively, in patients with decreased subcutaneous absorption, 2 μg of desmopressin acetate is given intravenously over one minute, and the duration of action, as judged by increased urine osmolality, is 12 hours or more (Rembratt, Graugaard-Jensen et al. 2004). DDAVP is safe for both the mother and the fetus when administered during pregnancy (Ray 1998).

For the vast majority of patients with DI, desmopressin is readily available, safe, and effective. Nevertheless, with partial DI and/or if the amount of available desmopressin is limited (Thurman, Halterman et al. 2003), the addition of other drugs that increase AVP release, enhance AVP effect on the kidneys (both of which require at least some endogenous AVP secretion), or directly decrease the urine output independent of AVP is rarely necessary. However, these agents, such as chlorpropamide, carbamazepine, clofibrate, thiazide diuretics, or NSAID, are less effective and associated with more adverse effects than desmopressin.

5. Conclusion

DI from post-traumatic hypopituitarism is documented as a potential contributor to morbidity and, possibly, mortality. As the above discussion shows, we suggest and note that

1. Greater awareness of these possible complications of TBI and appropriate testing are encouraged.
2. Assessment of the integrity of AVP secretion, and hypothalamic-pituitary axis is crucial to ensure the survival and the optimal rehabilitation of TBI patients.
3. Physicians should also present clinical symptoms of anterior or posterior pituitary dysfunction, not only for patients with severe TBI who need to be screened, but also for patients with minimal brain injury (Estes and Urban 2005).
4. The identification and the appropriate timely management of hormone deficiencies, such as the replacement and supplementation of desmopressin, are crucial to optimize patient recovery from brain injury, improve quality of life, and avoid long-term adverse outcomes of untreated hypopituitarism.
5. By monitoring pituitary function over time, planning appropriate hormonal replacement for brain-injured patients who acquired hypopituitarism is possible. This program requires tight collaboration with rehabilitation doctors and neurosurgeons.

6. Acknowledgment

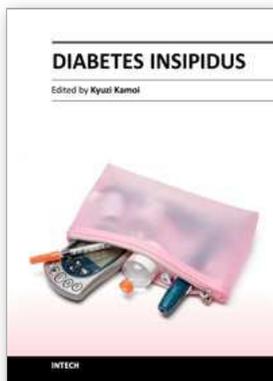
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Edited by Prof. Kyuzi Kamoi

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The first chapter of the book reports on the management of Langerhans cell histiocytosis (LCH)-induced central diabetes insipidus and its associated endocrinological/neurological sequelae in the national survey. The next chapter addresses DI and head injuries. Next, the management of neuroendocrine instability during maintenance of potential organ donors is described. Organ transplants have gradually increased worldwide. To have maintenance of appropriate potential organs, AVP is needed. Furthermore, nephrogenic DI-the potential therapeutic drugs and analysis of membrane protein stability is the topic of the next two chapters, followed by new insights into the diagnosis and management of pregnancy-related DI. The seventh chapter reports on the problems with differential diagnosis in a case of central DI in a female patient with bipolar disorder. The lithium treatment usually resulted in nephrogenic DI. Finally, over the last years, the development of MRI imaging on the pituitary gland with the stalk and hypothalamus has advanced. The final chapter interprets imaging techniques in DI in detail.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
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InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821