Rehabilitation Practice and Science

Volume 32
Issue 3 *Taiwan Journal of Physical Medicine and Rehabilitation (TJPMR)*

Article 5

12-31-2004

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Primary Adrenal Insufficiency Developing After Traumatic Brain Injury: A Case Report

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There have been isolated reports in the literature of the natural history and less than complete knowledge of the epidemiology and the pathophysiology of endocrine alteration occurring after traumatic brain injury (TBI). This article describes one primarily adrenal-dysfunction patient with severe TBI who had no evidence of present or prior adrenal autoimmune disease, infection, hemorrhage, or malignancy. It is suggested that this distinct condition can be labeled as "primary adrenal insufficiency (PAI) developing after TBI". (Tw J Phys Med Rehabil 2004; 32(3): 141 - 145)

Key words: primary adrenal insufficiency, traumatic brain injury

INTRODUCTION

Primary adrenal insufficiency (PAI) is deficiency of cortisol and aldosterone with elevated plasma adrenocorticotropic hormone (ACTH) due to autoimmune disease, trauma, infection or neoplasm of the adrenal glands.[1] Most of the symptoms of PAI, such as weakness, fatigue, anorexia, nausea, hypotension and hyperpigmentation, are nonspecific and usually occur insidiously.[2] Although various endocrine abnormalities have been described with TBI, including the syndrome of inappropriate anti-diuretic hormone (SIADH), diabetes insipidus, and anterior pituitary insufficiency, and the pathophysiology has been proposed with TBI-related pituitary and/or hypothalamic injury,[3] an isolated report of PAI following TBI has been published in medical literature.[4]

In this article, we describe a severe TBI case suffered from subacute-onset PAI and term this distinct condition as "PAI developing with TBI" to distinguish it from PAI secondary to such causes as autoimmune disease, trauma, infection or neoplasm. We propose theories regarding the pathogenesis and emphasize the concern with endocrine status in the TBI population and the need for further study to elucidate this entity. It is particularly important because of the good prognosis and excellent chance for recovery if patients are properly managed.

CASE REPORT

A 71-year-old man fell down accidentally, resulting in severe TBI. Cranial computed tomography (CT) scan revealed right subdural hematoma and intracranial hemorrhage. After an emergent craniotomy and evacuation of subdural hematoma, the patient was transferred to our rehabilitation facility three weeks later. At the beginning of comprehensive rehabilitation program, his Rancho Los

Submitted date: 29 January 2004. Revised date: 25 May 2004. Accepted date: 4 June 2004.

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Amigos Medical Center Level of Cognitive Functioning[5] was 4, concomitant with confusion and agitation. During initial comprehensive rehabilitation course, the patient's functional status gradually improved. Unfortunately, his confusion worsened suddenly with episodes of agitation in which he violently struck at medical staffs and his family members to resist any attempts of moving him. The cognitive insufficiency with poor memory and attention significantly influenced his compliance with the rehabilitation program. There was no fever, respiratory symptoms or gastrointestinal discomfort. On physical examination, there was no evidence of fluid overlaod or dehydraion, hyperpigmentation, or hypotension. Medications prescribed were phenytoin, nicardipine, captopril, dyphylline, and magnesium oxide. To eliminate any possibility of medication side effects, phenytoin was stopped without precipitating further seizure attacks. Second cranial CT scan showed no presence of hydrocephalus.

Laboratory data of complete blood count and differential count, C-reactive protein, and urinalysis was in normal range. Renal function tests showed blood urea nitrogen level of 15mg% and creatinine level of 0.9mg%. The plasma sodium level was worsened from 139mEq/L to 125mEq/L and the plasma potassium level elevated from 3.8mEq/L to 5.8mEq/L, while the plasma osmolality was 256mosm/Kg. The urine sodium level was 37mEq/L and urine potassium level 13.5mEq/L, while the urine osmolality was 409mosm/Kg. Normal thyroid function tests were performed with thyroid-stimulating hormone (TSH) of 1.4μU/mL, thyroxin (T4) of 10.9μg/dL, and triiodothyroinine (T3) radioimmunoassay of 96.4 ng/dL. Baseline morning cortisol level, at lower level, was 8.7 μg/dL, and plasma ACTH elevated to 73pg/mL. Corticotropin stimulation was performed to administer 250μg cosyntropin intravenously and measure plasma cortisol levels at baseline of 9.5μg/dL, then 30 minutes later, of 10.7μg/dL; an increase of 1.2μg/dL. PAI was diagnosed. Further evaluation with renal sonograph showed no evidence of adrenal hemorrhage or mass.

During the first week of cortisol replacement therapy with 10mg prednisone and 0.1mg fludrocortisone, the patient's confusion and episodes of agitation were mitigated markedly. At the same time he was more compliant with the comprehensive rehabilitation course. His Rancho Los Amigos Scale of Cognitive Functioning level was also improved from 4 to 5. Table 1 depicts the patient's functional status that was evaluated by Barthel index.[6] We compared his functional status before and after cortisol replacement therapy for a one-week period.

DISCUSSION

PAI is the primary inability of the adrenal gland to elaborate sufficient quantities of cortisol and aldosterone. There are a number of etiologies that could result in PAI. The most frequent cause is idiopathic autoimmune adrenalitis.[1,7-9] Adrenal parenchymal infections or

Table 1. Functional status evaluated by Barthel index at the time before cortisol replacement compared to 1 week after replacement

	before replacement	1 week after replacement
Feeding	0	5
Grooming	0	5
Bowel control	0	5
Bladder control	0	5
Wheelchair transfer	0	10
Toilet transfer	0	5
Dressing	0	5
Bathing	0	0
Level walking	0	0
Stairs	0	0
Total scores	0	40

malignancy and adrenal hemorrhage may lead to PAI. Several rare-inherited syndromes such as familial adrenal insufficiency, adrenoleukodystrophy and adrenomyeloneuropathy could be associated with PAI.[2] Findings in adrenal failure are nonspecific and chronic, including anorexia, nausea, vomiting, weight loss, weakness, fatigue, orthostatic hypotension and hyperpigmentation. Volume depletion, hyponatremia and hyperkalemia are common. Without a high index of suspicion, the diagnosis is missed easily.

A comparison between our case with another published in 1997[4] is shown in Table 2. The symptoms of PAI in our patient were obscure, with subacute-onset, during postacute rehabilitation course despite acute post-injury. Evidence of adrenal parenchymal idiopathic atrophy, hemorrhage, infection or tumors was not found either. The distinct condition suggests a causal relationship between PAI and TBI. For the body's ability to face with stresses such as trauma, infection and surgery, the hypothalamic-pituitary-adrenal axis plays an important role.[1] It has been reported that lower basal plasma cortisol concentration and impaired plasma cortisol response to a single corticotropin-releasing hormone stimulation in nonsurvivors were compared with survivors of severe sepsis.[10] The hypothesis that the stress to TBI is beyond the ability of the hypothalamic-pituitary-adrenal axis to cope, and causes primary endocrinologic organ dysfunction, instead of TBI-related pituitary and/or hypothalamic injury is suggested.

It is also possible that the onset and progression of the patient's PAI developed naturally after TBI, and the medication effect, which increases the catabolism of cortisol, may worsen signs and symptoms of PAI. There are anticonvulsants such as Phenobarbital and phenytoin, and other medications such as rifampin that induce liver cytochrome P450 enzymes.[2,11]

Table 2. Comparison of our case with Webster's case published in 1997.[4]

	Our case	Webster's case
Patient	71-year-old male	31-year-old male
Accident	Falling-down	Jet-ski
TBI classification	Severe TBI	Severe TBI
Transfer to rehabilitation facility	3 weeks after injury	1 month after injury
Rancho Los Amigos Medical Center Level of Cognitive Functioning at the time of transfer	4	5
Medical complications at the time of transfer	Hypertension	Early seizure, bilateral upper extremity deep venous thromboses, tracheostomy and percutaneous gastrostomy
Comprehensive rehabilitation course	Improved then worse with episodes of agitation	Persistent confusion, agitation, orthostasis, dizziness, and nausea
PAI clinical course	Manuscript of acute adrenal insufficiency developed within the subacute stage after TBI	Manuscript of chronic adrenal insufficiency developed within the subacute stage after TBI
PAI diagnosis algorithm approach	Hypoosmolatic hyponatremia and hyperkalemia with normal thyroid function and lower cortisol and elevated ACTH with abnormal ACTH stimulation test	Hypoosmolatic hyponatremia and hyperkalemia with normal thyroid function and normal cortisol with abnormal ACTH stimulation test
Treatment	10mg prednisone and 0.1mg fludrocortisone	Prednisone and fludrocortisone
Functional status evaluation	Rancho cognitive level from 4 to 5 & Barthel index from 0 points to 40 points 1 week after treatment	Improved with transfer, mobility, activities of daily living, attention and nutritional status 2 weeks after treatment

The diagnosis of PAI in TBI patient is not an easy job. Difficulty in diagnosis is two-fold. First, the process in which TBI patients recover from non-responsive status to resolution of post-traumatic amnesia (PTA) is important. Many patients demonstrate agitated and restless behavior.[12,13] The agitation is characterized by confusion, labile emotion, excessive motor activity, and in some cases, aggression. The period of agitation is generally transient. If these patients are under effective treatment, they will regain some ability to retain new memories. Furthermore, agitation can be an expression of an underlying medical problem, and agitated patients are often in poor compliance with therapy. Possible medical complications, such as electrolyte imbalances, seizure activity, sleep disturbances, discomfort due to musculoskeletal injury or post-traumatic hydrocephalus may exacerbate patients' confusion, which should be researched and well treated.[13]

Another reason is that SIADH and other endocrine abnormalities in the brain-injured patients are more and more common. 20% of patients with severe head injury were suffered from one or more hormone-level disturbances in a screening protocol.[11] SIADH is not only the most common endocrine abnormality happened in TBI patients but also the most common cause of hyponatremia in TBI patients. However, SIADH and PAI may cause similar changes in osmolality and electrolytes in plasma and urine, with more hyperkalemia in PAI.

The epidemiology, the natural history, and the pathophysiology of endocrine dysfunction in TBI survivors with various severities of injury, or longitudinally during recovery have remained controversial. The mechanisms between endocrine dysfunction and TBI are still uncertain. In order to establish a better rehabilitation program to significantly improve TBI patients' mental and physical function, further study of the endocrine status and mechanisms of endocrine dysfunction in TBI survivors is necessary.

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腦外傷併發原發性腎上腺功能不全：病例報告

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對於腦外傷病人於腦傷後體內內分泌改變的自然病程、流行病學及病理生理學只有少數的報告。本文報告一位無腎上腺自體免疫病、感染、出血及惡性腫瘤病史的嚴重腦外傷患者發生原發性腎上腺功能不全，呈現腦外傷引發原發性腎上腺功能不全的狀況。此特定病況或可稱之為「腦外傷併發原發性腎上腺功能不全」。（台灣復健醫誌 2004; 32(3): 141 - 145）

關鍵詞：原發性腎上腺功能不全(primary adrenal insufficiency)，腦外傷(traumatic brain injury)

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