Traumatic brain injury and adrenal insufficiency: morning cortisol and cosyntropin stimulation tests

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Abstract

Introduction: Adrenal insufficiency (AI) has a great impact on the prognosis of patients with traumatic brain injury. There is a lack of consensus regarding the diagnostic criteria of AI. In these patients with acute stress we compared fasting cortisol, low and high dose cosyntropin stimulation tests to assess adrenal function in patients with moderate to severe traumatic brain injury.

Material and methods: This multicenter, cross-sectional study recruited 50 consecutive patients (aged between 15 and 70 years old) with moderate to severe traumatic brain injury who survived more than 5 days after the event. The patients' adrenal function was assessed using the fasting cortisol, 1 and 250-µg ACTH stimulation tests.

Results: More cases of AI were detected by the 1-µg ACTH stimulation test compared to those detected by the basal serum cortisol level and 250-µg ACTH stimulation test. The κ test showed no agreement between these tests. The incidence of AI in the first 10 days after traumatic brain injury varied from 34% to 82% according to the various definitions of AI. The incidence of hypotension and need for vasopressors was higher in the patients diagnosed by the 250-µg ACTH stimulation test ($p < 0.0001$).

Conclusions: The incidence of secondary AI in moderate to severe traumatic brain injury seems to be high. A combination of stimulation test (either 250 or 1 µg) and basal cortisol level may improve diagnostic ability compared to either test alone. Hence performing both tests for the assessment of adrenal function in patients with traumatic brain injury is recommended.

Key words: traumatic brain injury, adrenal insufficiency, cosyntropin test.

Introduction

It is known that critically ill patients have an elevated cortisol level, yet some of these patients have insufficient cortisol production in proportion to the seriousness of their disease. Indeed, the cortisol level, whether relatively high or normal, may be inadequate for the physiological stress in some stressful conditions, reducing the patient's ability to cope with any additional stress [1]. In the setting of an intensive care unit (ICU), it is still extremely difficult to diagnose adrenal insufficiency (AI) in the majority of cases.

Traumatic brain injury (TBI) is one of the multiple etiologies of secondary adrenal insufficiency [2-7]. The TBI is an important cause of mortality in adult patients [8] and is reported with an annual incidence rate of 200 in 100,000

people in developing countries [9]. Hypopituitarism was reported to occur in 35% to 80% of patients in rehabilitation centers following head injury, with AI accounting for approximately 30% to 50% of these cases [7].

There is a paucity of data on the adrenal function in the early post-traumatic period (< 10 days), when the initiation of therapeutic management is crucial [7].

The absence of a widely accepted definition of an abnormal hypothalamic-pituitary-adrenal axis response in critically ill patients urged us to utilize various types of tests and also evaluate the agreement of different diagnostic tests. Moreover, we assessed the incidence of AI and its occurrence in relation to the severity of injury and mechanism of the trauma and ICU stay.

Material and methods

Prospectively, we studied 50 consecutive patients 15-70 old with moderate to severe traumatic brain injury who survived more than 5 days after the event, based on the Glasgow Coma Score (GCS), admitted to the neurosurgery ICU in 4 tertiary hospitals. Patients were eligible for inclusion in the study if they had suffered from severe or moderate traumatic brain injury according to the initial GCS. The exclusion criteria consisted of recent or long-term use of steroids, past history of head trauma or radiotherapy, preexisting pituitary and hypothalamus gland surgery, and pregnancy at the time of testing.

For each patient, the following information was recorded: age, sex, vital signs, mechanisms of trauma (road accidents, falls, etc.), total ICU stay and mortality, vasopressor/inotropic support, blood electrolyte levels (sodium/potassium), cerebral imaging findings, and the use of phenytoin, etomidate, and propofol.

In the GCS scoring, a score of 13 to 15 was regarded as mild, 9-12 as moderate, and ≤ 8 as severe TBI [10]. The cosyntropin stimulation tests with a low dose (1 µg) and high dose (250 µg ACTH) (adrenocorticotropin hormone) were performed at the end of the 1st week after head injury. The blood samples were taken at 8:00 AM for basal serum cortisol and ACTH, and then a low-dose ACTH stimulation test was done using 1 µg tetracosactrin (Synacthen Novartis England) intravenously. Serum samples were also obtained for cortisol at 30 and 60 min after the injection of 1 µg cosyntropin. One hour later, the test was repeated with 250 µg cosyntropin (high-dose stimulation test).

No commercially low-dose cosyntropin (1 µg) vial was available; hence a 1 µg solution was prepared from a 250 µg vial by injecting 1 ml of the diluents into the vial of cosyntropin to produce a 250-µg/ml solution and withdrawing 0.2 ml (i.e., 50 µg cosyntropin) and injecting it into a vial containing 24.8 ml of sterile normal saline solution to produce a 2 µg/ml solution, then 0.5 ml (1 µg cosyntropin) was immediately injected intravenously [1]. The dilution process was carried out by trained staff.

The blood samples were instantly separated and kept frozen at –70°C until they were assayed. All the cortisol levels were measured via the enzyme radioimmunoassay (RIA) (Immunotech, Radiova, Prague). The intra-assay CV for the serum cortisol samples was ≤ 5.8% and the inter-assay CV was ≤ 9.2%. The ACTH plasma level was measured using the Immunotec kit with a normal range of 9-52 pg/ml.

The definition of AI was based on the guidelines published in the year 2003; AI was considered when a random cortisol level was less than 15 µg/dl and it appears to be unlikely when a random cortisol measurement is more than 34 µg/dl. For patients with cortisol levels between these two values, a poor response to corticotropin test tends to indicate the possibility of AI and a need for stimulation tests. After the injection of cosyntropin, an increase of less than 9 µg/dl in cortisol indicates the likelihood of AI and an increase of more than 9 µg/dl rules out AI [11].

Recently published guidelines defined AI in critically ill patients as a delta total serum cortisol of < 9 µg /dl after 250 µg ACTH stimulation test or a random total cortisol of <10 µg/dl [12].

Primary and secondary AI were differentiated according to the ACTH results. Patients with a baseline cortisol level < 15 µg/dl and ACTH level < 9 pg/ml were considered to have secondary AI, patients with basal cortisol < 15 µg/dl and an ACTH level within 9-52 pg/ml were likely to have secondary AI.

The study was approved by the Ethics Committee of the Endocrine and Metabolism Research Center of our institute and written informed consent was obtained from all the patients or their families.

Statistical analysis

All the quantitative variables were presented as median (IQR). A κ test was used to assess the agreement between all the tests. The data were compared using the Mann-Whitney U test, *t*-test and Fisher exact test as appropriate. A value of $p < 0.05$ was considered statistically significant. SPSS for Windows standard version 13 was used for statistical analysis.

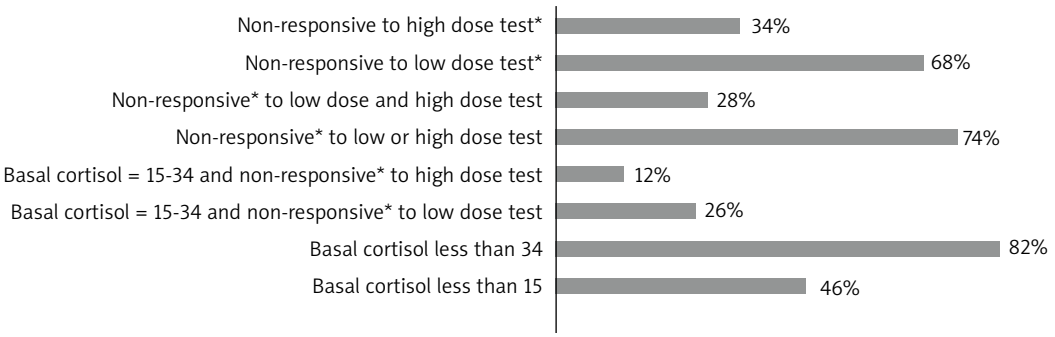
Results

Between June 2007 and December 2008, serum cortisol level and high and low dose ACTH tests were performed during the first 10 days on 50 patients admitted in ICU with a diagnosis of traumatic brain injury. The demographic, clinical, and laboratory characteristics of the patients with and without adrenal insufficiency are depicted in Table I. The incidence of AI varied according to different definition criteria (Figure 1).

Table I. Demographic, clinical, and laboratory characteristics (total number = 50) of the patients with traumatic brain injury (TBI) with and without adrenal insufficiency

Variables	Non-adrenal insufficiency	Adrenal insufficiency*	Value of *p*
Number of subjects	*n* = 5	*n* = 45	
Age [year] Median (IQR)	36 (33)	34 (25.5)	0.31
Male	5 (100%)	38 (84%)	0.99
Type of injury:			0.74
RTA	3 (60%)	30 (67%)	
Fall	2 (40%)	11 (24%)	
Other	0	4 (9%)	
Severity of injury:			0.99
Moderate (GCS 9-13)	1 (20%)	13 (29%)	
Severe (GCS < 9)	4 (80%)	32 (71%)	
Brain CT scan finding:			0.135
SAH	2 (40%)	4 (9%)	
ICH	2 (40%)	18 (40%)	
Mixed (SDH and ICH)	1 (20%)	23 (51%)	
Skull fracture	1 (20%)	16 (36%)	0.65
Brain edema	1 (20%)	15 (33%)	1
ECT	1 (20%)	18 (40%)	0.63
ICU admission days Median (IQR)	8 (23)	9 (11.5)	0.85
Hyponatremia (Na < 135 meq/l)	1 (20%)	6 (13%)	0.54
Phenytoin use	3 (60%)	32 (71%)	0.62
ACTH [pg/ml] Median (IQR)	29 (36.88)	13.5 (16.13)	0.3
Mortality	4 (80%)	15 (33%)	0.062

**AI definition: according to basal cortisol < 15 µg/dl or cortisol increase lower than 9 µg/dl after stimulation tests (1 µg/dl or 250 µg/dl) at 30 and 60 min. RTA – road traffic accident, SAH – subarachnoid hemorrhage, ICH – intracerebral hemorrhage, SDH – subdural hematoma, ECT – extra-cerebral trauma, ICU – intensive care unit*



**ACTH stimulation test non-responsive: cortisol increase after high dose (250 µg/dl) or low dose (1 µg/dl) (at 30 or 60 min) ACTH stimulation test less than 9 µg/dl. Various definitions [µg/dl]*

Figure 1. Incidence of adrenal insufficiency in patients with traumatic brain injury (TBI) according to various definitions

The κ agreement coefficient for AI according to the low-dose and high-dose stimulation tests is 0.175, which is in favor of the two tests' disagreement (Table II). The κ agreement coefficient between combined diagnosed tests of AI is shown in Table III. Disagreement was also evident between the basal cortisol level and the other two tests (κ –0.2 and 0.1, respectively).

Eighteen percent of AI patients with a baseline cortisol level < 15 µg/dl and ACTH level < 9 pg/ml were considered to have secondary AI and 28% with basal cortisol < 15 µg/dl and an ACTH level within 9-52 pg/ml were likely to have secondary AI.

All the AI patients diagnosed with the 250-µg stimulation test had higher rates of hypotension (systolic BP ≤ 100 mm Hg) and use of vasopressor agents (> 5 µg/kg/min of dopamine or > 0.02 µg/kg/min of norepinephrine for at least 24 h) (p-value = 0.00) (Table IV).

Seventy-one percent of the AI patients in this study used phenytoin 300 mg/day. The use of phenytoin did not significantly affect the baseline cortisol concentrations (t-test, p-value = 0.47). None of the patients took heparin or propofol.

Despite a normal response to the 1-µg stimulation test, 3 patients did not respond to the 250-µg stimulation test; a laboratory error might be the reason.

It is noteworthy that there were no side effects after the ACTH injection. Moreover, the research team was blinded to the test results and the possible treatment for the AI by the ICU physicians.

Discussion

In our study, 46% of the patients who had a baseline cortisol level > 15 µg/dl and 4% who had a baseline cortisol level > 34 µg/dl did not respond to one of the stimulation tests. There is no consensus about what precisely constitutes AI. Whereas some authors argue that a random cortisol concentration can define AI, others maintain that the response to the stimulation test is more appropriate. This lack of concordance can bring uncertainty and confusion [7].

In other words, when the cortisol level is within the normal range AI cannot be ruled out completely. However, AI patients are unlikely to have a cortisol base beyond the normal range. When there is doubt about the appropriate function of the hypothalamic-pituitary-adrenal axis, dynamic tests should be performed [1] in relative AI (primary or secondary), there is usually an increase in the production of cortisol but it fails to create a sufficient response to stress [13].

We demonstrated disagreement between the two stimulation tests in our study. Although disagreement is lower between some combined tests it is advisable that AI should be considered when either the baseline cortisol level or the stimulation test is abnormal (Table III).

A literature review revealed different aspects of 1 and 250-µg ACTH tests in the diagnosis of AI. The Streeten *et al*. study showed that the 1-µg ACTH test is more sensitive in patients who are in a non-critical condition [14]. The high sensitivity of the 1-µg stimulation test allows for false positive cases. Furthermore, they found that solely relying upon the ACTH test (250 µg) could lead to the non-diagnosis of AI and grave consequences for the patients. The higher sensitivity might be due to the more physiological level of ACTH in this test such that only normal adrenal can respond to it. Had we performed only the 250-µg stimulation test and baseline cortisol, we might have missed some cases with mild to moderate AI; and conducting only the low-dose test might result in over-diagnosis and unnecessary treatment. Some authors have even

Table II. Measure of agreement between 250- and 1-µg/dl ACTH stimulation tests for adrenal insufficiency diagnosis in patients with traumatic brain injury

	1 µg ACTH test	250 µg ACTH test	Total
Adrenal insufficiency (number)*	14	20	34
Non-adrenal insufficiency (number)	3	13	16
Total	17	33	50

*κ = 0.175. *Adrenal insufficiency – cortisol increase after high-dose (250 µg/dl) or low-dose (1 µg/dl) (at 30 or 60 min) ACTH stimulation tests less than 9 µg/dl*

Table III. Measure of agreement between base cortisol < 15 µg/dl or high-dose ACTH stimulation tests and base cortisol < 15 µg/dl or low-dose ACTH stimulation tests for adrenal insufficiency diagnosis in patients with traumatic brain injury

	Baseline cortisol < 15 µg/dl or 1 µg ACTH test		Total
	Adrenal insufficiency (number)*	Non-adrenal insufficiency (number)	
Baseline cortisol < 15 µg/dl	29	2	31
or 250 µg ACTH test	14	5	19
	43	7	50

*κ = 0.231. *Adrenal insufficiency – cortisol increase after high-dose (250 µg/dl) or low-dose (1 µg/dl) (at 30 or 60 min) ACTH stimulation tests less than 9 µg/dl*

Table IV. Comparison of hypotension and therapeutic management between patients with traumatic brain injury according to different definitions of adrenal insufficiency

Variable	Base cortisol*			Low dose ACTH test**			High dose ACTH test**		
	< 15 (n = 27)	> 15 (n = 23)	Value of p	Normal (n = 16)	Abnormal (n = 34)	Value of p	Normal (n = 33)	Abnormal (n = 17)	Value of p
Systolic BP < 110 mm Hg [%]	18%	21.7%	0.77	18%	20%	0.88	10%	41%	0.007
Vasopressor use [%]	18%	21.7%	0.77	18%	20%	0.88	10%	41%	0.007

**Baseline cortisol < 15 µg/dl. **Abnormal low-dose or high-dose ACTH stimulation tests: cortisol increase after high-dose (250 µg/dl) or low-dose (1 µg/dl) (at 30 or 60 min) ACTH stimulation tests less than 9 µg/dl*

suggested the substitution of the 1-µg test with the 250-µg test for the evaluation of central AI [15].

Since the insulin tolerance test (ITT, gold standard) is contraindicated in critically ill patients, there is a paucity of data for determining the sensitivity and specificity of these two tests.

In one study on septic shock patients with a baseline cortisol level > 34 µg/dl and an increase in the cortisol level < 9 µg/dl following the stimulation test, a higher mortality rate was observed in comparison with patients who had a similar baseline cortisol level and an increase in the cortisol level > 9 µg/dl following the stimulation test [12]. Hence we speculate that an evaluation of adrenal function according to the basal cortisol without the ACTH stimulation test is not enough.

In our study, the rate of hypotension and vasopressor use was higher in the AI patients diagnosed by the 250-µg stimulation test compared to the 1-µg stimulation test. This might be due to the fact that while the 250-µg stimulation test can determine the clinically evident AI patients (symptomatic cases such as hypotensive patients) the 1-µg stimulation test can reveal functional or relative AI (near to the physiological dose). The Cohan *et al*. study showed that hypotension and the need for vasopressors in AI traumatic brain patients were more common [16].

The incidence of AI in the whole cohort of acute traumatic brain injury (moderate to severe) patients was between 34% and 82% according to the different definition criteria of AI. Although patients with mild head injury were excluded from our study, it should be noted that pituitary dysfunction tends to happen in some of these patients as well [17, 18].

In our study, there was no significant relationship between the severity of head injury and the incidence of AI; it may be due to the small sample size and also the exclusion of patients with mild TBI. It has been speculated that severity of TBI is a risk factor for occurrence of panhypopituitarism and secondary adrenal insufficiency [17-19].

In our study, the mortality rate, although not statistically confirmed, unexpectedly was higher in the non-AI group. Further studies with larger sample sizes are required for an accurate conclusion.

The small sample size of our cohort is a limitation of our study. The prohibition of insulin tolerance test (ITT) as the gold standard test was a drawback of our study. Dilution of the contents of a 250-µg ACTH 1-24 ampoule by inexperienced personnel could be troublesome. Hence the dilution should be carried out by a trained staff according to a very strict protocol or a commercial form of 1-µg ACTH ampoule should become available [20]. The lack of commercially available vials of 1-µg ACTH was another drawback.

In conclusion, AI should be assessed in the acute phase of patients with head injury, so that an appropriate treatment modality can be provided for clinical and subclinical cases. A combination of stimulation test (either 250 or 1 µg) and basal cortisol level may improve diagnostic ability compared to either test alone. Hence, we recommend performing both tests for the assessment of adrenal function in traumatic brain injury patients. AI should be considered when either the baseline cortisol level or the stimulation test is abnormal.

Since undiagnosed AI is life-threatening and increases the mortality rate, patients with hypotension requiring vasopressor agents in the first week after trauma should receive sufficient amounts of corticosteroids after full assessment with both random cortisol and dynamic tests. The treatment should be tapered according to the results of the stimulation test (250-µg) during the recovery period. Future studies with a larger sample size including patients with mild head injury and their follow-up after improvement are required for a concise conclusion on the diagnostic and therapeutic management of this population.

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