Original Article

Relative Adrenal Insufficiency amongst Hospitalized Mild to Moderate Acute Ischemic Stroke Patients

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Abstract

Introduction: Acute ischemic stroke is a stressful condition where there is marked increase in the production of cortisol. In the past, adrenal insufficiency in critically ill patients had been shown to be associated with significant morbidity and mortality. To date, there have been no studies performed to determine its prevalence among patients with acute ischemic stroke.

Objectives: The aim of this study was to determine the prevalence of relative adrenal insufficiency in acute ischemic stroke by utilizing low dose (LD) and standard dose (SD) synacthen tests and to correlate it with inpatient hospital morbidity and mortality.

Method: Fifty-eight patients who fulfilled the diagnosis of acute ischemic stroke within 72 hours from the onset of a stroke were subjected to LD (1μg) synacthen test (LDST) and two hours later to SD (250 μg) synacthen test (SDST).

Result: Based on an increment of less than 250 nmol/L after LDST, 38 (65.5%) patients had relative adrenal insufficiency. However, using similar criteria with the SDST, only 18 (31.0%) patients had relative adrenal insufficiency. Three patients died during the study period and they had a tendency to have high baseline cortisol levels. The diagnosis of relative adrenal insufficiency in general was not associated with any other significant clinical outcomes.

Conclusion: This is the first study demonstrating the prevalence of relative adrenal insufficiency amongst acute ischemic stroke patients. Utilizing the LDST, relative adrenal insufficiency was found more sensitive in detecting relative adrenal insufficiency in patients with acute ischemic stroke as compared to SDST.

Keywords: Adrenal insufficiency, ischemic stroke, low dose synacthen test, synacthen test, standard dose synacthen test

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Introduction

Stroke is a clinical syndrome defined as a "rapidly developing clinical signs of focal or global disturbance of cerebral function with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin".[1] It is a global health problem and is the second commonest cause of death.[2] The severity of earlier neurological impairment following ischemic stroke has an influence on short-term and long-term outcomes.[3] The Scandinavian Stroke Scale (SSS) is a simple tool to monitor neurological progress in which a low SSS score is a predictor of early neurological deterioration following acute ischemic stroke.[4] A low SSS score at baseline or within 24 hours of an ischemic stroke is a strong predictor of death within 30 days.[5]

It is recognized that the acute adaptive adrenal response to stress is a shift away from mineralocorticoid production with up to six fold increase in glucocorticoid production.[6] Circulating cortisol levels in critically ill patients are more than three times higher than healthy individuals as a result of reduced hepatic degradation, loss of the normal diurnal pattern of secretion, decreased cortisol binding globulin (CBG) and increased receptor sensitivity.[6–8] This acute phase typically lasts for a few hours or days. There is dissociation between high plasma cortisol and low adrenocorticotropin (ACTH) levels suggesting non-ACTH mediated mechanisms for the regulation of the adrenal cortex during this phase.[6] Glucocorticoids are important to maintain vascular tone and endothelial integrity.[8] Adequate adrenal function is essential to overcome any form of stress conditions. Deficiency of cortisol during critical illness has been associated with increased morbidity and mortality. [9] The prevalence of adrenal insufficiency in critically ill medical patients varies from 10% to 77%.[10–12] This wide variation was due to the different criteria used to define adrenal insufficiency and the severity of illness.[10–12]

Subnormal corticosteroid production during critical illness without structural defects in the hypothalamic-pituitary-adrenal axis has been termed "relative adrenal insufficiency".[13] It is due to high levels of inflammatory cytokines causing direct inhibition of adrenal cortisol synthesis and mediating tissue-specific corticosteroid resistance.[13] Relative adrenal insufficiency can develop during the course of an illness and is usually transient.

Synacthen test is the standard test used to assess adrenal function. Standard or conventional dose (250 μg) synacthen test (SDST) is

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mostly used in critically ill patients.[8] In normal subjects, 5 μg or 10 μg of human corticotrophin will stimulate the adrenal cortex maximally.[14] Crowley, et al. have shown that most normal subjects have maximum cortisol responses after low dose (1 μg) synacthen test (LDST).[15] The LDST test also has been shown to be sensitive for detecting adrenal insufficiency in both critically ill and non- critically ill patients and patients with defects in the HPA axis.[16–18] Bornstein, et al. showed that LDST is the best test to diagnose adrenal insufficiency in critically ill patients.[18] Studies in critically ill patients have shown either a baseline cortisol level of <500, 690, or 825 nmol/L or an incremental response of less than 250 nmol/L after cosyntropin stimulation predicted a poor outcome and identified patients who responded favorably to glucocorticoid administration.[8,19,20]

In an earlier published report, we demonstrated the prevalence of adrenal insufficiency in patients with acute coronary syndrome using baseline cortisol, LDST and SDST.[21] Up to date to our knowledge, there have been no published studies looking at the prevalence of relative adrenal insufficiency in acute ischemic stroke patients. The aim of this study was to determine the prevalence of relative adrenal insufficiency in patients with acute ischemic stroke using two different forms of synacthen test.

Patients and Methods

Patients and tests

This study was conducted in the medical department, Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM). Ethical approval was granted by the Clinical Research and Ethics Committee of our institution. Patients gave informed consent prior to participation in the study. For patients who were too ill to give individual written consent, the closest relatives available gave written informed consent on behalf of the patient. During the period between August 2011 and February 2012, 58 patients who were diagnosed with stroke within 72 hours of event onset, based on clinical and/or radiological evidence, were consecutively recruited.[22] None of the patients had systemic inflammatory response syndrome (SIRS) infection, underlying chronic kidney disease (CKD) or history of pituitary, adrenal, or liver diseases. None were taking traditional medications or drugs known to influence glucocorticoid secretion (i.e., rifampicin, ketoconazole, other anti-fungal agents or anticonvulsants).

The assessments of neurological and functional status were determined on admission using the SSS.[23] The SSS consists of 9 items: consciousness; eye movements; arm motor power; hand motor power; leg motor power; orientation; speech; facial palsy and gait. The scores range from 0 (poorest health status) to 58 (best health status). The patients were divided into 2 groups based on stroke severity on admission. Severe stroke was defined as SSS score ≤30 and SSS scores >30 were categorized as mild-to-moderate stroke.

The LDST was performed on the first morning after their admission between 8 a.m. to 9 a.m. and blood for cortisol was collected before the injection of 1μg ACTH (0_{LD}) with subsequent sampling at 30 minutes (30_{LD}) and 60 minutes (60_{LD}). Two hours later, SDST was performed by administering 250 μg of ACTH and blood samples were collected at 0 min (0_{SD}), 30 minutes (30_{SD}), 60 minutes (60_{SD}) and 90 minutes (90_{SD}), respectively.[12,24] The 2-hour interval between the 2 doses of ACTH was to allow the cortisol levels to return to baseline before the second test performed.[12,24] The order of the tests was maintained throughout the study as the SDST may have resulted in a more sustained rise in cortisol levels that would have required increasing the time interval between the 2 tests. The 1 μg ACTH was prepared by diluting 1 mL of the ACTH 250 μg to 49 mL with normal saline. This solution was shaken giving a final concentration of 1μg ACTH equal to 0.2 mL of the solution.[24]

Definitions of response criteria

The diagnosis of relative adrenal insufficiency was made using the following established criteria:

1. Baseline cortisol levels of <525 nmol/L[25]
2. Failure to mount a cortisol response following LDST and SDST:

a. The LDST:

i. Increment of cortisol <250 nmol/L[26]

ii. Peak cortisol of <700 nmol/L [26]

b. The SDST:

i. Increment of cortisol <250 nmol/L[11]

ii. Peak cortisol of <700 nmol/L[26]

The cortisol response to LDST was determined by subtracting the serum cortisol level at 0 minute (0_{LD}) from the level at 30 minutes (30_{LD}). Similar calculations were made to determine the response at 60 minutes after LDST and at 30 and 60 minutes after SDST.

Cortisol and ACTH assays

Serum cortisol and plasma ACTH were stored at -20°C until assayed. Both samples were measured using commercially available chemiluminescent enzyme immunoassays based on the Immulite Operator's Manual (Diagnostic Product Corp, Los Angeles, CA, USA). The quality control (QC) of cortisol samples were 91–141 nmol/L for low level, 254–386 nmol/L for moderate level and 750–1126 nmol/L for high level. While the QC of ACTH samples were 28–40 pg/mL for low level and 450–518 pg/mL for high level. All samples were analyzed in one batch to avoid interassay variation.

Statistical analysis

The data were analyzed using SPSS program version 19. Differences in cortisol levels intra and inter-groups were analyzed with Wilcoxon signed-rank and Wilcoxon-Mann-Whitney tests, respectively. Spearman correlation coefficient was used for calculation of correlation. A *P*-value <0.05 was considered significant.

Result

Subjects characteristics

Of the 58 patients, 41 (70.7%) were male and 17 (29.3%) females. The majority of the patients were Chinese 35 (60.34%), followed by 14 (24.14%) Malay, 5 (8.62%) Indian and the remaining 4 (6.90%) were of other ethnicities. The mean age of the patients was 66.62 ± 10.41 years, ranging between 43–87 years. The mean blood pressure (BP) and heart rate (HR) of the study cohort were 164±31.33 mmHg and 80 ± 22 bpm, respectively. Forty-two (72.4%) patients presented with first episode of stroke and 16 (27.6%) patients presented with recurrent stroke. The clinical characteristics are summarized in Table 1.

The majority [46 patients (79.3%)] had mild to moderate stroke (SSS > 30), and 12 (20.7%) patients had severe stroke (SSS ≤30). At presentation, about 49 (84.5%) patients had GCS between 13

Table 1. Clinical characteristics of study population.

Variable		Number (%)
Blood pressure (mmHg)	Systolic	164 ± 31.33*
	Diastolic	87.93 ± 26.00*
Heart rate		80 ± 22*
Co-morbidities	Diabetes mellitus	33(56.9)
	Hypertension	47(81.0)
	Dyslipidemia	29(50.0)
	Smoker	26(44.8)
	Vascular disease	17(29.3)
Numbers of co-morbidities	0 risk factor	3(5.17)
	1 risk factor	7(12.07)
	2 risk factors	20(34.48)
	3 risk factors	12(20.69)
	4 risk factors	11(18.97)
	5 risk factors	5(8.62)
Concomitant medication	CCB	20(34.5)
	Beta blocker	19(32.8)
	Diuretic	5(8.6)
	ARB	7(12.1)
	ACE inhibitor	18(31.0)
	Sulfonylurea	12(20.7)
	Biguanides	16(27.7)
	Insulin	8(13.8)
	Statin	32(55.2)
	Fibrate	5(8.6)
	Antiplatelet	26(44.8)
*Data express in mean ± SD		

Table 2. Laboratory indices of study population.

Variables	Median (IQR)
Albumin (g/L)	41.4 ± 5.0*
Baseline ACTH(pg/L)	16.8 (6.94–25.18)
Baseline cortisol (0_{LD}) (nmol/L)	427.5 (272.5–626.0)
Baseline cortisol (0_{SD}) (nmol/L)	422.0 (270.0–533.5)
* variable express in mean ± SD; 0_{LD} refers to 0 min cortisol levels from time of LDST and 0_{SD} refers to 0 min cortisol levels from time of SDST; IQR = interquartile range	

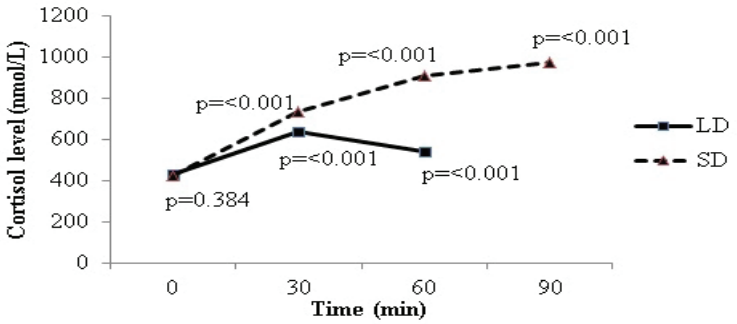

Figure 1. The above graph showed cortisol responses following low dose (LD) and standard dose (SD) synacthen tests.

and 15 (mild) whereas 9 (15.5%) patients had GCS between 8 and 12 (moderate). None had GCS <7. The median duration of stroke prior to performing the synacthen tests was 31.5 (23.75–53.5) hours. The earliest presentation of stroke was after 8 hours and the latest presentation was 72 hours. The length of stay in ward ranged from 2 to 21 days with a median of 5 (3–7) days. The co-morbidities and concomitant medications of study population are as shown in Table 1.

Biochemical results

The median baseline cortisol and ACTH levels were 427.5 nmol/L (272.5–626.0) and 16.8 pg/mL (6.94–25.18), respectively (Table 2). There was no correlation between baseline cortisol at 0_{LD} and the onset of stroke and (r = -0.109, $P = 0.415$) as well as with baseline ACTH level (r = 0.074, $P = 0.398$). There was a positive correlation between baseline cortisol level and age (r = 0.287, $P = 0.023$) but not with stroke severity. There was a significant difference between the median cortisol at 0 minute compared to 30 and 60 minutes using LDST and SDST ($P < 0.001$) (Figure 1). There was no significant difference between baseline cortisol levels at 0_{LD} and 0_{SD} (427.5 vs. 422 nmol/L, $P = 0.384$) (Figure 1).

The prevalence of relative adrenal insufficiency was 36 (62.1%) when a baseline cortisol level (0_{LD}) of <525 nmol/L was used as criterion. However, when the standard diagnostic criteria (an in-

crement cortisol post-corticotrophin <250 nmol/L) were used, 38 (65.5%) patients had relative adrenal insufficiency by the LDST and 18 (31%) patients by the SDST. If peak cortisol response <700 nmol/L to LDST and SDST were taken, 34 (58.6%) and 21 (36.2%) patients were noted to have relative adrenal insufficiency, respectively.

Morbidity and mortality

Seven (12.1%) patients developed medical complications during the acute stay. Five (8.6%) patients had pneumonia and two (3.4%) patients developed upper gastrointestinal bleeding. There were 3 (5.2%) deaths during the hospital stay, all of which presented with the first episode of stroke. The mean age of these patients and the duration of stroke were 63.67 ± 12.05 years and 23.33 ± 21.57 hours, respectively. Two of them had severe SSS and one patient had mild SSS. The mean length of hospital stay in patients who died was 14.33 ± 10.69 days. The baseline cortisol was 425 nmol/L (262 –618) in the survivor group and 673 (361–866) nmol/L in the non-survivor group ($P = 0.171$).

Discussion

In this study, the prevalence of relative adrenal insufficiency among acute stroke patients using the LDST was 62.1% (based on baseline cortisol <525 nmol/L), 65.5% (based on increment of cortisol <250 nmol/L) and 58.6% (based on peak cortisol <700 nmol/L). The prevalence was 1.5 to 2 times higher when using LDST compared to SDST. Overall, the prevalence of adrenal insufficiency was consistent with previous studies done in critically ill patients, ranging between 10% to 77%.[10–12] To our knowledge, this is the first study looking at the prevalence of relative adrenal insufficiency in stroke population.

Our patients achieved their maximum cortisol response at 30 minutes following LDST and this was consistent with the previous study in acute coronary syndrome and stressed patients.[17,21] All of them received LD followed by SDST with a two-hour interval between the two doses. There was no significant difference demonstrated between cortisol 0_{LD} compared to 0_{SD} suggesting that the cortisol level has reached its baseline value prior to SDST and hence the earlier LDST performed do not affect the SDST results.

The increment of cortisol levels persisted even after 90 minutes of stimulation with SDST indicating a prolonged response. This was also noted in previous studies among patients with acute coronary syndrome and critically ill patients in ICU.[21,24] Thus, it is not recommended to begin with SDST as the first test. This prolonged cortisol response will inevitably interfere with the result of the second test. As this observation was not seen with the LDST results, performing the LDST first should not affect the results of the subsequent SDST.

The median duration of presentation of stroke was 31.5 hours which is longer than the earlier study done by Christensen, et al.[27] This may be due to the lack of public awareness of stroke, health consciousness and access to medical facilities. In the present study, the mortality rate noted was 5.2%. This was in accordance with the study done by Koennecke, et al. which showed that the overall in-hospital mortality was 5.4% among acute stroke patients who were admitted to 14 stroke units in Germany.[28] There was no significant difference between mortality and relative adrenal insufficiency noted. The presence of relative adrenal insufficiency appeared not to be related to death during hospital admission in our cohort. The cause of death in our cohort was mainly due to complications from the stroke itself. There was no correlation documented between cortisol levels and severity of stroke using the SSS program. In contrast, Christensen, et al. showed positive correlation between stroke severity with cortisol levels in patients within 24 hours of stroke onset.[27] This discrepancy may be due to differences in sample size, onset of stroke and severity of the stroke.

There was no correlation noted between ACTH and cortisol levels, consistent with previous studies.[18,21] The ACTH levels were low relative to cortisol levels; the exact mechanism for this dissociation is unknown.[18,21] A decrease in vascular supply to the hypothalamus and/or pituitary during vasospasm of a cerebrovascular accident may be a cause. Furthermore, this pituitary-adrenal dissociation also suggests that the cytokines produced under stress condition might be responsible for the adrenocortical activation and cortisol production.[18] Further evaluation would be needed in this area.

In conclusion, this is the first study that looked at the prevalence of relative adrenal insufficiency in acute ischemic stroke patients based on two doses of synacthen tests. The prevalence of relative adrenal insufficiency was noted to be twice higher using the LDST, suggesting that LDST is more sensitive in detecting cases of relative adrenal insufficiency in stroke patients. There was no significant association between SSS with relative adrenal insufficiency. This is perhaps driven by the fact that majority of our stroke patients presented with milder forms of the disease with very few fatalities.

Study limitation

Our study is limited by its small sample size due to financial constraints.

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