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General Medicine

A STUDY ON THE CORRELATION BETWEEN SERUM CORTISOL LEVELS AND SEVERITY OF ACUTE ISCHEMIC STROKE.

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ABSTRACT **INTRODUCTION:** There are many clinical variables like symptom severity and advanced age which are identified as potential predictors of outcome in patients with acute stroke. But there is an immense need to detect a biomarker for predicting the outcome of acute stroke. The stress response that occurs after the event of acute stroke causes the activation of the hypothalamic–pituitary–adrenal (HPA) axis. Certain studies have found that increased serum cortisol level in patients with acute stroke is related to larger infarct volume, greater stroke severity and poor outcome, including death **AIM AND OBJECTIVE:** To assess the relationship of single serum cortisol levels to the severity of acute ischemic stroke. **MATERIALS AND METHODS:** About 50 new cases of acute ischemic stroke patients, within 72 hours of the acute neurological event, who were admitted to the Chalmeda Anand Rao institute of medical sciences, Karimnagar, Telangana were included in the study. The study was conducted for 6 months.CT Brain was taken during admission to confirm acute ischemic stroke. NIHSS (National Institute of Health Stroke Scale) scores for all the patients were assessed for severity at the time of admission. Serum cortisol levels were measured the next day early morning. After 15 days, the functional outcome of the patients was assessed using the Modified Rankin Scale. The correlation between serum cortisol levels and stroke scales is assessed byChi–Square Test. All statistical analyses are performed using SPSS (software package used for statistical analysis) package. **RESULTS:** Of the 50 cases, the serum cortisol level of 23 cases was within normal limits(</=690nmol/L) of which 65.2% had NIHSS scores of less than or equal to 6 and 34.8% of the cases had NIHSS scores more than 6. As the NIHSS score of less than or equal to 6 is considered to be a minor stroke, it is obvious from the above findings that most of the cases with normal cortisol levels had no major stroke. The remaining 27 cases had elevated serum cortisol levels.100% of the cases with serum cortisol levels of more than 690nmol/L had NIHSS scores above 6. With a p-value of <0.001, this is found to be statistically significant. As the NIHSS score above 6 is considered to be moderate to severe stroke, it is obvious from the above observation that nearly all cases with elevated cortisol levels had moderate to severe stroke. Of the 50 cases, serum cortisol levels of 23 cases were within normal limits(,/=690nmol/L)of which 78.3% had MRS scores less than or equal to 3 and 21.7% had MRS scores more than 3. Since the MRS score is a measure of functional outcome and any score less than or equal to 3 is considered to have a favourable outcome, it is clear from the above findings that most of the cases with normal serum cortisol had a favourable outcome with minimal neurological impairment. And in the remaining 27 cases which had serum cortisol levels of more than 690 nmol/L, 3.7% had an MRS score of less than or equal to 3 and 96.3% had an MRS score of more than 3. With a p-value of <0.001, this is statistically significant. Since an MRS score of more than 3 is associated with a bad outcome, most of the cases with elevated serum cortisol had a poor outcome with severe neurological impairment. **CONCLUSION:** Among the patients with acute ischemic stroke, high serum cortisol levels at the time of admission correlate with, Clinical severity which is assessed by the National Institute of Health Stroke Scale and Poor prognosis and functional outcome after 15 days which is assessed by the Modified Rankin Scale.

KEYWORDS : Acute ischemic stroke, HPA axis, serum cortisol, clinical severity, Functional outcome, stroke scales.

INTRODUCTION

There are many clinical variables like symptom severity and advanced age which are identified as potential predictors of outcome in patients with acute stroke. But there is an immense need to detect a biomarker for predicting the outcome of acute stroke. The period that ensues after the event of acute stroke can be regarded as a reaction to a stressful event. This stress response causes the activation of the hypothalamic–pituitary–adrenal (HPA) axis[1] and sympathetic nervous system. In an acute stroke, the first measurable alterations are the endocrine changes because of the alteration in HPAaxis

REGULATION OF CORTISOL SECRETION: ROLE OF ACTH:

The basal secretion of cortisol and the stress-provoked increased secretion are both under the dependency of ACTH from the anterior pituitary. In addition to the prompt increase in the secretion of cortisol, ACTH also causes increased responsiveness of the adrenal gland to the subsequent doses of ACTH.

CIRCADIAN RHYTHM:

The plasma cortisol trends rise and fall in response to the secretion of ACTH which occurs in irregular bursts throughout the day. In the early morning, the bursts are more frequent and between 4 AM and 10 AM occur 75% of the daily production of cortisol. This diurnal rhythm in the secreting pattern of ACTH is seen in patients with adrenal insufficiency receiving constant doses of glucocorticoids. The biological clock responsible for the diurnal ACTH secretion is situated in the suprachiasmatic nuclei of the hypothalamus. If the day is lengthened experimentally to more than 24 hours, then the adrenal cycle also lengthens, but the rise of ACTH secretion occurs during the period of sleep.

THE STRESS RESPONSE:

Morning plasma ACTH levels in a healthy resting human are about 25pg/ml. The amount of ACTH produced exceeds the amount necessary to produce maximal cortisol output, during times of severe stress[2].

In emergencies, the increase in ACTH secretion is mediated through the hypothalamus by the release of Corticotrophin Releasing Hormone(CRH). The neurons in the paraventricular nuclei produce this polypeptide and are secreted in the median eminence. Then it is transported to the anterior pituitary through the portal hypophyseal vessels, where it stimulates ACTH secretion. Increased secretion in response to various stresses is blocked if the median eminence is destroyed.

Paraventricular nuclei are the place of convergence for many afferent nerve pathways from many parts of the brain. An increase in ACTH production in response to fear, anxiety, apprehension, and emotional stresses is mediated by the fibres from the amygdaloid nuclei. The drive for the diurnal rhythm is provided by input from the suprachiasmatic nuclei.

Impulses ascend to the hypothalamus through the nociceptive pathways and the reticular formation trigger increased ACTH secretion in response to injury. Inhibitory input is triggered by the baroreceptors via the nucleus of tractus solitarius.

CORTISOL FEEDBACK: ACTH secretion is inhibited by the free glucocorticoid levels.

The rate of ACTH secretion is determined by the summation of two opposing forces. The sum of the neural and possibly other stimuli converging through the hypothalamus to increase ACTH secretion, and the magnitude of the braking action of glucocorticoids on ACTH

secretion, which is proportionate to their level in the circulating blood.

ROLE OF CORTISOL IN STRESS AND INFLAMMATION:
Any type of stress be it neurogenic or physical, stimulates the anterior pituitary to secrete ACTH which in turn increases the adrenocortical secretion of cortisol within minutes. The fast mobilization of fats and amino acids by cortisol helps the damaged tissues to utilize them for energy and synthesis of new proteins and other essential substances like pyrimidines, purines and creatine phosphate, which are essential for the reproduction and maintenance of cells. The effect of cortisol is thus preferential in mobilizing the proteins that are labile to make amino acids available for the cells that are in need to produce substances necessary for life. Bradykinin, prostaglandin, histamine and other proteolytic enzymes are released from the site of injury that activates the inflammatory process. Cortisol exerts anti-inflammatory effects in three ways:

Early stages of inflammation are blocked even before the inflammation begins Rapid resolution of inflammation if it has begun already Increased rapidity of healing

MEASUREMENT OF CORTISOL:
Cortisol can be measured in heparinised plasma or serum. It can also be measured in urine. Cortisol analysis in saliva can be used as a surrogate marker for its measurements in plasma or serum.

LIMITATIONS:
- There are limitations to the diagnostic utility of the single cortisol measurement, which are due to, Diurnal variation in cortisol concentration.
- Cortisol elevation during stress
- Episodic cortisol secretion.
- Stress can make the cortisol levels in patients with adrenal insufficiency fall within the reference range, similarly, patients with Cushing's disease can have normal values of cortisol levels, despite the loss of diurnal variation, during the day.

REFERENCE CORTISOL VALUES:
From 8.00 am to 12 noon: 138–690 nmol/L
From 12 noon to 8 pm: 138–414 nmol/L
From 8.00 pm to 8.00 am: 0–276 nmol/L

CORTISOL AND STROKE:
There is an early and massive activation of the Hypothalamo-Pituitary-Adrenal axis(HPA) seen in the hyperacute phase of stroke. The biphasic pattern of response is observed characteristically. ACTH and cortisol are increased concomitantly initially. In the second phase, cortisol levels remain increased though there is a rapid decrease in ACTH levels.

The above-mentioned pattern is explained by the fact that the initial activation of the HPA axis is soon followed by very strong cortisol-induced suppression of levels of ACTH. Also the increased susceptibility of the adrenal gland maintains elevated cortisol levels. Surprisingly the adrenal gland hyperresponsiveness to ACTH is also shown in the early recovery stage of the postoperative state.

The proinflammatory cytokines that are released in tissue injury possess an ACTH or corticotrophin-releasing hormone(CRH) like activity which explains the strong response of the adrenal gland in the absence of an increase of ACTH parallelly and its relation to the extent of brain damage.

The concept of neurotoxicity of the HPA hormones is established in many in vivo and in vitro studies. It clearly outlines that cortisol causes damage to the brain by exacerbating the hypoxic injury to astrocytes and the neurons[3,4,5], and by Impeding glucose uptake and its metabolism in the brain Higher cortisol levels are linked to cognitive dysfunction because hypercortisolism can cause the reinforcement of ischemic damage to the hippocampal neurons[6,7,8,9]. Also it is linked with higher morbidity and poorer functional outcome in stroke patients[10,11]. Also, it is found that repeated stresses are common in patients with acute ischemic stroke in the form of infections, emotional reactions, and cardiovascular complications. The adrenal sensitivity to ACTH can be increased by repeated stresses. And hence hypercortisolism can be prolonged.

ROLE CYTOKINES IN CORTISOL AXIS ABNORMALITIES AFTER STROKE:
Proinflammatory cytokines[12,13] are released in a cascade after brain infarction. It is the TNF alpha which starts the cascade after ischemia, which in turn activates interleukin 1 and 6. Sympathetic nervous system activation also contributes to the effect.

There are multiple levels at which interleukin – 6[14,15] can be regulated in acute ischemic stroke. Also, any psychological and physical stressors can elevate the interleukin – 6 levels because of the activation of the hypothalamic-pituitary-adrenal axis. After the event of acute stroke, many inflammatory cytokines are released from the peripheral blood cells.

There is also a finding that abnormal leptin[16] levels with flattening of diurnal variations in patients with stroke. There is more evidence that leptin[17] is associated with neuroendocrine balance which also includes cortisol axis regulation. There are studies which show that initial IL-6 levels and abnormal diurnal rhythmicity of cortisol levels can predict stroke outcomes.

MATERIALS AND METHODS STUDY DESIGN:
STUDY GROUP: All new cases of acute ischemic stroke admitted in Chalmeda anand rao institute of medical sciences, Karimnagar, within 72hrs of acute neurological event satisfying the inclusion and exclusion criteria.

TYPE OF STUDY: Cross-sectional study
SAMPLE SIZE: 50

PLACE OF STUDY: Department of General Medicine, Chalmeda anand rao institute of medical sciences, Karimnagar, Telangana.

INCLUSION CRITERIA:
1) Patients in the age group above 18 years.
2) Patients proven to have acute ischemic stroke admitted within 72 hours of the onset of the neurological event (by CT brain plain).

EXCLUSION CRITERIA:
1) Age less than 18 years
2) Pregnancy.
3) Liver disease
4) Patients who are not on the following drugs: Immunosuppressants, steroids, Rifampicin, and Phenytoin.
5) History of malignancy.
6) Hemorrhagic stroke.
7) Acute febrile illness
8) Major surgery within 3 weeks.

STATISTICAL ANALYSIS:
The mean values of the parameters are calculated by the Independent sample – t-test.

The correlation between serum cortisol levels and stroke scales is assessed by Chi–Square Test.

All statistical analyses are performed using SPSS (software package used for statistical analysis) package.
A p-value of less than 0.05 is considered to be statistically significant.

RESULTS:
TABLE: 1. AGE WISE DISTRIBUTION OF STROKE

AGE IN YEARS	NUMBER OF CASES	PERCENTAGE
31-40	4	8
41-50	3	6
51-60	10	20
61-70	17	34
71-80	12	24
81-90	4	8
TOTAL	50	100

TABLE 2: SEX-WISE DISTRIBUTION OF CASES

Sex	Number of cases	Percentage
MALE	30	60
FEMALE	20	40

TABLE 3: MEAN CORTISOL LEVEL IN MALE AND FEMALE CASES

Sex	N	Mean cortisol	Standard deviation	Standard error of the mean

MALE	30	631.07	138.199	25.663
FEMALE	20	659.14	194.324	42.405

TABLE 4: NUMBER OF DIABETICS AND NON-DIABETICS AND MEAN CORTISOL LEVELS:

	Number of cases	Percentage	Mean cortisol	SD	Standard error of the mean
DIABETICS	14	28	590.15	193.461	53.657
NON DIABETICS	36	72	661.38	149.227	24.533

TABLE 5: NUMBER OF HYPERTENSIVE AND NON-HYPERTENSIVE AND MEAN CORTISOL LEVELS:

	Number of cases	Percentage	Mean cortisol	SD	Standard error of the mean
Hypertensive	20	40	657.75	174.853	39.098
Non-Hypertensive	30	60	632.93	156.614	28.594

TABLE 6: NUMBER OF CASES WITH NIHSS SCORE </= 6 AND >6

	Number of cases	Percentage
NIHSS </= 6	15	30
NIHSS >6	35	70
TOTAL	50	100

TABLE 7: NUMBER OF CASES BASED ON MODIFIED RANKIN SCALE </= 3 OR >3

	Number of cases	Percentage
MRS</= 3	19	38
MRS > 3	31	62
TOTAL	50	100

TABLE 8: CORRELATION OF SERUM CORTISOL LEVELS AND NIHSS SCORE

NIHSS score on admission	SERUM CORTISOL IMMOL/L			
	</= 690		>690	
	No of cases	Percentage	No of cases	Percentage
</= 6	15	65.2	0	0
> 6	8	34.8	27	100
TOTAL	23	100	27	100

TABLE 9: CORRELATION OF SERUM CORTISOL LEVELS AND MRS

MRS on admission	SERUM CORTISOL IN MMOL/L			
	</= 690		>690	
	No of cases	Percentage	No of cases	Percentage
</= 3	18	78.3	1	3.7
> 3	5	21.7	26	96.3
TOTAL	23	100	27	100

DISCUSSION:

A total of 50 patients were enrolled in the study who were proven to have Acute Ischemic Stroke by CT Brain which was taken at the time of admission. The minimum age of the patients is 31 years and the maximum age was 85 years. Among the 50 patients,34% of the acute ischemic stroke occurred in the age group of 61 to 70 years. And about 60%were males and 40 % were females.

The mean cortisol level was 631.07 in males. The mean cortisol level in females was 659.14

Of the 50 cases, 28% were diabetics and 72% were non-diabetics. The mean cortisol level in diabetics was 590.15 7. The mean cortisol level in non-diabetics was 661.38 40% were hypertensives and 60% were normotensives. The mean cortisol level in hypertensives was 657.75. The mean cortisol level in normotensives was 632.93 30 % had CAD an 70 % did not have CAD. The mean cortisol level in cases with CAD was 612.92 The mean cortisol level in non-CAD was 652.32. Of the 50 cases 13 had systolic BP less than 140mmHg, 37 had systolic BP more than or equal to 140mmHg.ie., 26% had normal systolic blood pressure and 74% had elevated systolic blood pressure. Also, 35 had diastolic BP less than 90 mmHg and 15 had diastolic BP more than or equal to 90 mmHg.ie., 70 per cent had normal diastolic BP and 30% had elevated diastolic BP of the 50 cases, 6 had infarct in the Anterior cerebral artery territory and 42 had infarct in the middle cerebral artery territory and 2 had infarct in the posterior cerebral artery territory.ie., 12% had ACA territory infarct, 42% had MCA territory infarct, 2% had PCA territory infarct. It is clear that the majority of the cases had MCA territory infarct Of the 50 cases, the serum cortisol level of 23 cases was within normal limits (</=690nmol/L) of which 65.2% had NIHSS score of less than or equal to 6 and 34.8% of the cases had NIHSS score more than 6. As the NIHSS score of less than or equal to 6 is considered to be a minor stroke, it is obvious from the above findings that most of the cases with normal cortisol levels had no major stroke.

The remaining 27 cases had elevated serum cortisol levels.100% of the cases with serum cortisol levels of more than 690nmol/L had NIHSS scores above 6. With a p-value of <0.001, this is found to be statistically significant. As the NIHSS score above 6 is considered to be moderate to severe stroke, it is obvious from the above observation that nearly all cases with elevated cortisol levels had moderate to severe stroke. Of the 50 cases, serum cortisol levels of 23 cases were within normal limits(,/=690nmol/L)of which 78.3% had MRS scores less than or equal to 3 and 21.7% had MRS scores more than 3. Since the MRS score is a measure of functional outcome and any score less than or equal to 3 is considered to have a favourable outcome, it is clear from the above findings that most of the cases with normal serum cortisol had a favourable outcome with minimal neurological impairment. And in the remaining 27 cases which had serum cortisol levels of more than 690 nmol/L, 3.7% had an MRS score of less than or equal to 3 and 96.3% had an MRS score of more than 3. With a p-value of <0.001, this is statistically significant. Since an MRS score of more than 3 is associated with a bad outcome, most of the cases with elevated serum cortisol had a poor outcome with severe neurological impairment.

Also among the 50 cases, 5 cases showed mortality and had elevated serum cortisol (>690nmol/L) at the time of admission.

CONCLUSION:

Among the patients with acute ischemic stroke, high serum cortisol levels at the time of admission correlate with, Clinical severity which is assessed by the National Institute of Health Stroke Scale and Poor prognosis and functional outcome after 15 days which is assessed by the Modified Rankin Scale.

CLINICAL SIGNIFICANCE:

In humans, the adrenal stress response causes increased blood glucose, catabolism, and heart rate and potentiates ischemic neuronal damage. In acute ischemic stroke, these effects could induce secondary brain damage. Hypothalamic - Pituitary- adrenal axis alterations are one of the major stress-induced alterations after the event of cerebral ischemia.

Cortisol is an independent short-term marker of prognosis of functional outcome and death in patients with acute ischemic stroke even after the correction of confounding factors. Elevated cortisol after the onset of stroke is associated with morbidity, dependency and mortality. A combined model can however add significant information to the clinical score.

Since the early prediction of stroke outcome is very important for the allocation of therapeutic strategies, serum cortisol level measurement at the time of admission can add significant predictive information to the existing NIHSS score.

CONFLICT OF INTREST: NONE

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