

Study of Prevalence and Predictive Factors of Adrenal Insufficiency in Patients Admitted to Medical Intensive Care Unit in a Tertiary Care Hospital of North Karnataka

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ABSTRACT

Introduction: Adrenal insufficiency is a rare, but potentially lethal disease if left untreated. Symptoms, signs and biological markers associated with adrenal insufficiency are well established but often missed, affecting patient outcome. This study aimed to assess the prevalence of, and factors associated with adrenal insufficiency among patients admitted to medical ICU.

Material and Methods: All patients with suspected adrenal insufficiency in a medical ICU were screened with high-dose (250 µg) ACTH-stimulation tests. Cortisol values <550 nmol/l upon stimulation were considered diagnostic for adrenal insufficiency; history, clinical findings and biological parameters were recorded and analysed.

Results: 45 (22.06%) patients of the 204 assessed, had confirmed adrenal insufficiency, with a Male: Female sex ratio of 1:1.4; maximum in older age group (62.2%); mean age being 57.92 years with 35.6% diabetics and 31.1% hypertensives. Most had primary diagnosis of bacterial sepsis with 33.3% gram negative, 15.6% gram positive sepsis and 20% tuberculosis. 62.3% patients were in hypotension requiring vasopressor support, with increased incidence of associated hyperkalemia (57.8%), hyponatremia (62.2%) and acidosis (53.3%). Profound adrenal failure identified in 22.2%. The overall one week mortality 28.9%, despite optimal supportive management.

Conclusions: Confirmed adrenal insufficiency was observed in 22.06% of patients admitted in intensive care unit, associated and complicated by bacterial sepsis, including tuberculosis in 68.9% cases, with overall one week mortality of 28.9%. Combination of hypotension, hyperkalemia, hyponatremia and acidosis in an intensive care patient should prompt clinicians to suspect adrenal insufficiency, as early detection and optimal management would improve the overall outcome in such patients.

Keywords : Adrenal Insufficiency, Adrenal Failure, Hypotension, ACTH Stimulation Test, Glucocorticoid Therapy, Gram Negative Sepsis

INTRODUCTION

Adrenal insufficiency, caused by either primary adrenal failure (mostly due to autoimmune/ infective adrenalitis) or by hypothalamic-pituitary impairment of the corticotrophic axis (predominantly due to pituitary disease), is a potentially lethal disease if overlooked during acute settings.^{1,2} Main presenting symptoms such as fatigue, anorexia, and weight loss are nonspecific, hence under critical care settings; the relative importance of these symptoms is often ignored thus delaying the diagnosis. Though, the diagnostic work-up is well established, some pitfalls still remain, particularly in the identification of secondary adrenal insufficiency.³ Despite optimised life-saving glucocorticoid and mineralocorticoid-replacement therapy, health-related quality of life in adrenal insufficiency

is more severely impaired than previously thought.¹ Long-term management of patients with adrenal insufficiency remains a challenge, requiring an experienced specialist. However, all doctors should know how to diagnose and manage suspected acute adrenal failure.

The aim of this study was to assess the prevalence of, and factors associated with adrenal insufficiency among patients admitted to medical intensive care unit.

MATERIAL AND METHODS

Study population

All patients admitted in Medical Intensive Care Unit of our hospital between January 2015 and December 2016 and requiring an ACTH-stimulation test based upon clinical judgment were included. This study was approved by the Institutional Ethics Committee of our Institute.

Data Collection

All patients included in our study group, after applying inclusion and exclusion criteria, were assessed. Their detailed clinical history, including co-morbid conditions, physical signs including low blood pressure (<90 mmHg systolic and/or <60 mmHg diastolic blood pressure), the results of biological markers including hyperkalemia (> 5 mmol/l), hyponatremia (< 135 mmol/l), acidosis (pH<7.35), hypercalcaemia (>2.5 mmol/l) and ACTH tests were recorded in a pre-designed proforma. The primary diagnoses of the patients were recorded. Mortality was assessed for a week period. ACTH-stimulation test was considered as normal if any value of cortisol was ≥550 nmol/l.

STATISTICAL ANALYSIS

The data collected were subjected to Statistical analysis. Results were expressed as number of patients and (percentage) for qualitative data and as mean ± standard deviation for quantitative data.

RESULTS

During the study period, 451 patients admitted in the medical ICU

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| Patient characteristics | Observed values |
|---|--------------------------|
| Total No of MICU patients assessed. | 204 |
| Prevalence of Adrenal Insufficiency (study group) | 45 (22.06%) |
| Mean Age of study group | 57.92 yrs. (Range 22-71) |
| M:F sex ratio | 1:1.4 |
| Proportion of older age patients (>50 yrs.) | 28 (62.22%) |
| Comorbid illness | |
| Diabetes mellitus | 16 (35.56%) |
| Systemic Hypertension | 14 (31.11%) |
| Cardiovascular Disease | 4 (8.89%) |
| Liver Disease | 3 (6.67%) |
| Neurological Disease | 5 (11.11%) |
| Auto-Immune Disease | 2 (4.44%) |
| H/O Alcoholism | 15 (33.33%) |
| H/O Smoking | 5 (11.11%) |
| Primary diagnosis | |
| Gram (+) ve Sepsis | 7 (15.56%) |
| Gram (-) ve Sepsis | 15(33.33%) |
| Tuberculosis | 9(20%) |
| Deliberate Self Harm | 4(8.89%) |
| Snake bite | 3 (6.67%) |
| Vascular Causes | 2(4.44%) |
| Undiagnosed | 5 (11.11%) |

Table-1: Clinical characteristics of the patients with adrenal insufficiency

| Biological markers and mortality | Observed values |
|----------------------------------|-----------------|
| Hypotension | 28 (62.22%) |
| Acidosis | 24 (53.33%) |
| Alkalosis | 15 (33.33%) |
| Hyperkalemia | 26 (57.78%) |
| Hypercalcemia | 4 (8.89%) |
| Hyponatremia | 28 (62.22%) |
| Leucocytosis | 21 (46.67%) |
| Leucopenia | 5 (11.11%) |
| Profound adrenal failure | 10 (22.2%) |
| Mortality | 13 (28.89%) |

Definitions: Hypotension (<90 mmHg systolic and/or <60 mmHg diastolic blood pressure), Acidosis (pH<7.35), Alkalosis (pH>7.45), Hyperkalaemia (>5 mmol/l), Hyponatremia (<135 mmol/l), Hypercalcemia (Calcium >2.5 mmol/l), Leucocytosis (Total Count > 11000) and Leucopenia (Total Count < 4000). Profound adrenal failure was defined as Serum Cortisol < 100nmol/l after ACTH stimulation test. Results are expressed as number of patients and (percentage).

Table-2: Biological markers and mortality of patients with adrenal insufficiency

were assessed and 247 patients were excluded after applying the exclusion criteria. These patients were excluded because they were either using or had long term use of glucocorticoids, some were diagnosed cases of chronic glucocorticoid insufficiency, or on drugs interfering with hypothalamic-pituitary-adrenal axis or without valid written consents. The remaining 204 patients clinically suspected of adrenal insufficiency had an ACTH-stimulation test. Unexplained signs such as hypotension, hyperkalemia, metabolic acidosis or hyponatremia were the key signs used to order the ACTH-stimulation test in most

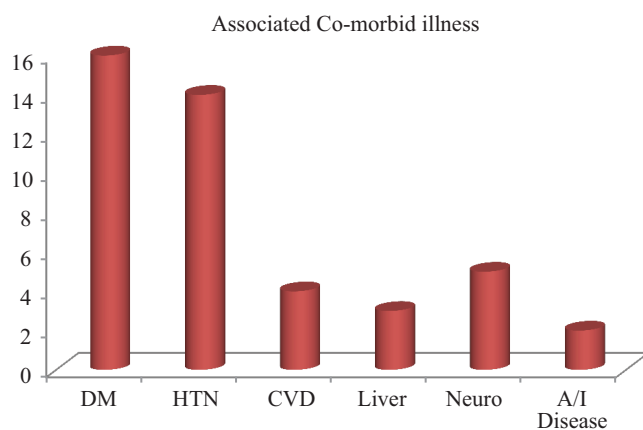


Figure-1: Comorbid illness associated with patients with adrenal insufficiency

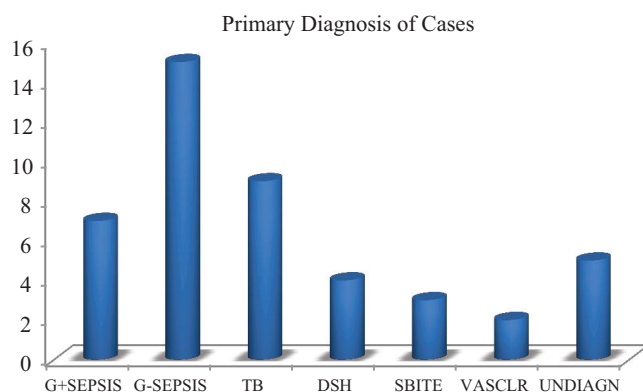


Figure-2: Primary diagnosis of patients admitted in MICU having adrenal insufficiency

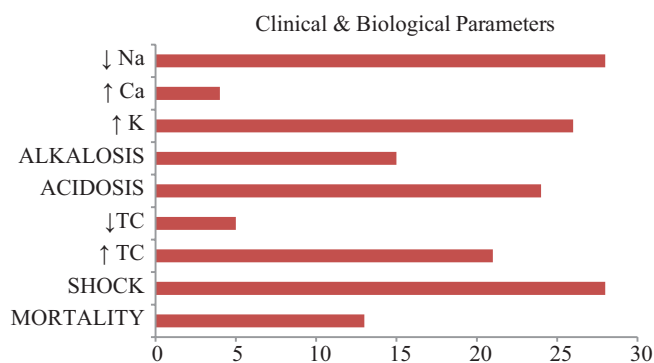


Figure-3: Biological markers and mortality associated with adrenal insufficiency

clinical situations. If adrenal failure was suspected, the ACTH-test was performed with syntropin 250µg iv and serum cortisol measuring after 30-60 minutes and in most cases, stress doses of glucocorticoid administrated for 48 hours. Out of 204 patients, 45 patients (22.06%) were diagnosed with adrenal insufficiency after ACTH-test and stress doses of hydrocortisone or prednisone were administrated and tapered for them.

Patient Characteristics

Among the 45 patients diagnosed as adrenal insufficiency, 19 were males and 26 females with a male : female sex ratio of 1:1.4. In our study group 62.2% (28 patients) were in the older age group (>50 years) compared to 37.8% (17 patients)

of younger patients (≤ 50 years). The mean age of the study group was 57.92 ± 11.1 years, ranging from 22-71 years. On scrutinising for other co-morbid illness in the past, 35.6% (16 patients) were found to be diabetic and 31.1% (14 patients) were hypertensive. Other illness prevalent in decreasing frequencies were neurological (11.1%), cardiovascular disease (8.9%), hepatic and renal disease (6.67%); only 4.4% (2 patients) were diagnosed cases of auto-immune disorder. (Autoimmune Thyroiditis, other as Pernicious Anaemia)

Among patients with adrenal insufficiency, maximum number, 33.3% (15 patients) were diagnosed as gram negative sepsis, following further workup. 20% (15 patients) were diagnosed as tuberculosis (both pulmonary and extra pulmonary together), 15.6% patients were diagnosed as gram positive sepsis, 8.9% patients were admitted for deliberate self-harm (DSH)-including poisoning and hanging, 6.7% for snake bite and 4.4% diagnosed as vascular etiology. For the remaining 11.1% patients, diagnosis was uncertain or not confirmed.

In our study, 62.3% (28) of patients were in hypotension requiring vasopressor support, all of them received replacement glucocorticoid therapy. Other biological parameter assessment in them showed, hyperkalemia in 57.8% (26 patients), hyponatremia in 62.2% (28 patients) and hypercalcemia in only 8.9% of patients. Arterial blood gas analysis was done; acidosis was observed in 53.3% (24) patients and alkalosis in 33.3%. Total leucocytes were raised ($> 11,000/\text{mm}^3$) in 46.7% of patients and leucopenia (total count $< 4000/\text{mm}^3$) in 11.1% of patients.

For the 45 patients that had a confirmed adrenal failure, ACTH levels were only available for eight patients, due to financial restraints. Out of those eight patients, six (13.3%) had combined low levels of cortisol and elevated ACTH levels, confirming the diagnosis of primary adrenal failure. The other two patients (4.4%) had combined low levels of cortisol and ACTH, confirming a secondary adrenal failure. Profound adrenal failure was identified for 10 patients (22.2%) with cortisol levels < 100 nmol/l.

On a short term follow-up (up to 1 week) of these 45 cases with confirmed adrenal insufficiency, 13 patients (28.9%) died despite optimal supportive management and glucocorticoids, of which 9 patients (69.2%) had profound adrenal failure.

DISCUSSION

The administration of supra physiologic doses of ACTH (250 μg) is the standard challenge to test the adrenal responsiveness. This test has been widely used and several studies have reported an excellent agreement between peak cortisol concentrations obtained during the test and in the gold standard insulin tolerance test.³ In our study, about two out of ten (22.06%) patients admitted in our intensive medical unit had an abnormal response to high-dose ACTH stimulation test.

We found that older adults had a higher rate of adrenal insufficiency than younger patients, consistent with other studies, that the relative importance of other health problems, particularly infections, which occurred in association with the adrenal insufficiency, varied with the age of the patient.⁴ Older patients with adrenal insufficiency are at risk of a number of health problems such as cardiovascular disease, osteoporosis, infections etc. A predisposition to infection, together with the importance of bacterial infection in the initiation of an adrenal

crisis, suggests that a low threshold for instituting antibiotic therapy in older patients with adrenal insufficiency may be warranted.⁵⁻⁷

In this study, we found that women represented approximately 58% of the critical patients with adrenal insufficiency, which is consistent with the male/female ratio seen in a Swedish study⁶ and may be a reflection of the underlying prevalence of adrenal insufficiency in the population.⁸

Approximately 48.9% of patients with adrenal insufficiency in our study had bacterial sepsis, among them 33.3% had gram negative sepsis, almost two fold, compared to 15.6% patients who had gram positive sepsis. Tuberculosis was found in 20% of cases. The impact of exposure to bacterial infections on patients with hypoadrenalism is two fold. First, a number of studies have demonstrated that hypoadrenal patients are at increased risk of bacterial infection.^{6,8,9} Second, the consequences of a bacterial infection in patients with hypoadrenalism differ from those experienced by patients with normal adrenal function. This is because systemic bacterial infection provokes a powerful inflammatory cytokine response stimulating the hypothalamic-pituitary-adrenal axis to produce a state of hypercortisolism. This, in turn, acts to reduce inflammation and prevent tissue damage. However, in the presence of cortisol deficiency, as is the case in Addison's disease, the absence of an increase in serum cortisol levels leads to an unrestrained inflammatory response, which results both in tissue damage and systemic effects, such as hypotension/shock and multi-organ failure.¹⁰

Low blood pressure was observed in more than half (62.2%) of the patients in our study. Low blood pressure remains a well-recognized sign of acute adrenal insufficiency, however, other clinical diagnosis responsible for low blood pressure should be ruled out.¹¹ Biological markers of the disease including Hyperkalemia, Hyponatremia And Metabolic Acidosis are well established biological markers of adrenal insufficiency. These biological markers were found in more than half of our study group.

In our study, 28.9% (13) patients died over one week, in spite of receiving optimal glucocorticoid replacement therapy and supportive management. Among them 69.2% (9) patients had profound adrenal failure. Despite optimal glucocorticoid replacement therapy, adrenal crisis remains one of the most common causes of death among patients with chronic adrenal cortical insufficiency.¹² The symptoms of adrenal crisis including fatigue, nausea, vomiting, and hypotension are non-specific, often leading to misdiagnosis. However, the prognosis of acute adrenal crisis critically depends on rapid parenteral administration of hydrocortisone (or other glucocorticoids) by the attending physician, regardless of the underlying illness.¹³ Notwithstanding the diagnostic advances and available steroid replacement therapy, adrenal insufficiency is still a potentially lethal condition.¹²

Our study has several limitations. First, we measured only the total cortisol and not the free cortisol. Free cortisol is thought to be more representative of the physiologic actions of cortisol because of the common findings of hypoalbuminemia in the critically ill patients.¹⁴ However, a recent study conducted by Annane et al.¹⁵ showed that free cortisol was not superior to total cortisol in diagnosing adrenal insufficiency in the critically-ill subjects. Secondly, the plasma ACTH values were not

collected for all individuals due to financial restraints and we could not discriminate between primary and secondary adrenal insufficiencies. Finally, we have done the high dose ACTH test only, which may identify only profound adrenal failure but not partial and subtle corticotropic failure that could have been detected in a low-dose (1 µg) ACTH stimulation challenge.

CONCLUSION

In this study, approximately 22% of suspected patients admitted in intensive care unit had adrenal insufficiency, defined by an abnormal response to high-dose (250 µg) ACTH-stimulation test, with ~28% mortality. Our results also suggest that adrenal insufficiency is associated and complicated by bacterial sepsis, including tuberculosis.

A high index of suspicion is required for diagnosing adrenal insufficiency, especially in critically ill patients. The combination of hypotension, hyperkalemia, hyponatremia and acidosis in an intensive care patient should prompt clinicians to suspect adrenal insufficiency, which otherwise is often missed, as early detection and optimal management would improve the overall outcome in such patients.

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