

10 Addisonian Crisis—An Emergency Overlooked

Abstract: Addisonian crisis is a life-threatening emergency due to acute deficiency of adrenocortical hormones which, if not diagnosed early and treated aggressively, is invariably fatal. One needs to be thoroughly conversant with the manifestations of this potentially fatal endocrine emergency which may vary from extreme lassitude and prostration with abdominal pain and nausea with vomiting to one of severe hypovolemic shock unresponsive to fluid and vasopressor therapy. Awareness of this life-threatening condition and its inclusion in the differential diagnosis of unexplained shock would go a long way in saving a catastrophic outcome as early institution of therapy with massive doses of steroids and fluids is amply rewarding.

Acute adrenal deficiency is classified based on its etiology – as ‘*Primary*’ when the pathology is in the adrenal itself, usually a catastrophic event like adrenal infarction or hemorrhage due to severe septicemia, especially meningococcal, HIV itself or the accompanying opportunistic infections which are emerging as one of the causes of chronic adrenal insufficiency and which may lead to acute insufficiency due to the stress of coexisting infections. Antiphospholipid antibody syndrome is now being recognized as an occasional cause of infarction or hemorrhage leading to adrenal crises. The ‘*Secondary*’ causes of adrenal crisis is due to the hypothalamopituitary disease – usually an infarction or hemorrhage into a pre-existing pituitary tumor – the ‘*pituitary apoplexy*’. But common cause of secondary adrenal insufficiency is due to the suppressed hypothalamopituitary axis occurring as a result of steroid therapy manifesting as acute deficiency in times of stress.

This review discusses the etiology and types of Addisonian crisis, its presentation, diagnosis and management. It also lists the guidelines for preventing this crisis in people who have compromised adrenal function.

INTRODUCTION

It is some one hundred fifty years ago that Thomas Addison described a syndrome of long-term adrenal insufficiency that develops over months or years characterized by weakness, fatigue, weight loss and hyperpigmentation, the classical Addison’s disease taught to medical students even on initiation into the complex world of medicine. But what was not stressed in earlier days is another life-threatening presentation with vomiting, abdominal pain and hypovolemic shock, termed as Addisonian crisis, a not uncommon medical emergency which is often not thought of. Failure to recognize this potentially fatal endocrine emergency in the early stages has a dismal prognosis for survival whereas prompt evaluation on clinical suspicion and early institution of aggressive therapeutic measures will be rewarding. It is proposed to briefly review this topic to remind ourselves the need to include it in the differential diagnosis of any condition with unexplained hypovolemic shock in its early stages.

DEFINITION

Addisonian crisis can be defined as a medical emergency characterized by extreme prostration, hypovolemic shock, irresponsive to fluid replacement and administration of vasopressors. It is caused by an abrupt or sudden failure on the part of adrenal cortex to produce cortisol in response to normal physiologic demands.¹ This failure could be due to destruction or defect of the adrenal cortex when it is termed ‘*primary*’ or due to a hypothalamopituitary disease or suppression of hypothalamopituitary-adrenal (HPA) axis when it is called ‘*Secondary*’.

Etiology and Pathophysiology

Table 1 lists the etiology of adrenal insufficiency- chronic and acute, both primary and secondary.^{2,3} It is to be stressed that though acute adrenocortical insufficiency is due to the causes listed under acute, it is important to remember that some of the chronic conditions on steroid replacement therapy with physiological doses may rapidly progress to acute insufficiency under stress - infective, traumatic, surgical or metabolic.

Primary Adrenocortical Insufficiency

Out of the etiological causes listed in the table under chronic adrenal insufficiency, tubercular infection of the adrenal glands is much more common than autoimmune disease in our setting unlike western countries where the latter accounts for most of the cases - 40% isolated and 60% part of polyendocrine syndrome. In the series from India approximately one-third of the patients with chronic tubercular adrenal disease presented in acute adrenal crises.⁴ Similarly in the series from North America where auto immune disease was the underlying cause the diagnosis was made only when the patients presented with an acute crisis during an intercurrent illness.⁵

As regards other infections that are listed there appears to be a distinct change in the scenario - especially in India where HIV is being increasingly encountered as one of the causes of adrenal insufficiency.⁶ Adrenal gland is the most commonly involved endocrine organ in patients infected with HIV, most of them being critically ill.⁷ Apart from direct involvement of the gland with HIV, potential etiologies of adrenal insufficiency include opportunistic infections associated with HIV : Cytomegalovirus (CMV), *Mycobacterium avium* intracellulare (MAI), *Mycobacterium tuberculosis*, cryptococcosis, histoplasmosis, toxoplasmosis and *Pneumocystis carinii*. In addition, malignancies like Kaposi's sarcoma and Non-Hodgkin's lymphoma can cause adrenal insufficiency. Medications that interfere with cortisone synthesis include ketoconazole, rifampin, phenytoin and megestrol acetate. Autopsy studies revealed involvement of the adrenals in more than 50% of patients with HIV infection.⁸ Risk factors for adrenal insufficiency included long duration of infection, CD4 counts less than 50 cell/cu mm and associated opportunistic infections - especially tuberculosis and CMV.⁹

The most dramatic and catastrophic adrenal crisis, however, is due to adrenal hemorrhage or infarction. The classic presentation described independently by Waterhouse and Friderichsen in the early nineties, which was termed purpura fulminans is due to meningococcal septicemia.¹⁰ In India, meningococcal septicemia with acute adrenal insufficiency occurs in epidemics especially in overcrowded dormitories and army barracks.¹¹ Other pathogens which may cause bilateral adrenal haemorrhage leading to acute adrenocortical insufficiency include *Streptococcus pneumoniae*, β -hemolytic streptococci, *Pseudomonas aeruginosa* and *Escherichia coli*.¹²

The other causes of bilateral adrenal hemorrhage are heparin induced thrombocytopenia, anticoagulant overdose and metastatic disease.¹³ Of the more recently described ones is the antiphospholipid antibody syndrome which is characterized by recurrent venous or arterial thrombosis with fetal loss in the females occasionally associated with collagen disorder. In a recent case review adrenal insufficiency due to bilateral adrenal hemorrhage due to haemorrhagic infarction was the first clinical manifestation of this syndrome. The authors concluded that screening for lupus anticoagulant and anticardiolipin antibodies is appropriate in all cases of adrenal hemorrhage and in adrenal insufficiency of uncertain cause.¹⁴

Secondary Adrenocortical Insufficiency

The underlying abnormality in secondary adrenocortical insufficiency is either a diseased hypothalamus or pituitary - more often the latter - or due to suppression of the HPA axis. Hypothalamic / pituitary lesions - neoplastic, ablative, traumatic, infective or autoimmune - can

affect the functional status of the adrenal cortex leading to chronic adrenal insufficiency which differs from primary adrenocortical insufficiency by the absence of hyper-pigmentation.

Acute adrenal crisis under secondary causes include pituitary apoplexy caused by sudden infarction or hemorrhage into the gland. Most cases of pituitary apoplexy involve pre-existing pituitary adenomas which may be precipitated by pregnancy, anticoagulation, head trauma or surgery.¹⁵ Postpartum pituitary necrosis-Sheehan's syndrome - occurs due to hypotension associated with peripartum bleeding leading to acute adrenal crisis.

A much more common secondary cause of acute adrenal insufficiency, however, is sudden or abrupt withdrawal of long term steroid therapy. The same emergency would occur if such a patient with compromised HPA axis develops a stressful event - be it infective, vascular, traumatic or surgical. Secondary adrenocortical insufficiency is relatively common due to extensive therapeutic use of steroids and failure to step up the therapeutic dosage in times of stress leading to acute insufficiency.

There is a basic difference in the pathophysiology of primary as against secondary adrenal insufficiency. While in primary, glucocorticoid and mineralocorticoids are both deficient, salt and water deficiency and hence hypotension is much more severe. In the secondary type it is the glucocorticoid deficiency which has its major effect on glucose metabolism and immune suppression.

Incidence of Acute Adrenal Crisis

The true incidence is not known but with widespread use of steroids resulting in suppression of HPA axis it is much more common especially in critical care units, than the reported incidence. In fact, in a study conducted on patients admitted to a critical care unit 31% had been demonstrated to have secondary adrenal insufficiency. Studies of critically ill patients with septic shock demonstrated adrenal insufficiency in 19-54% of patients.¹⁶ Bilateral adrenal hemorrhage was found only in 1.1% of 2000 consecutive general hospital autopsies but the incidence was 15% in patients dying of shock.¹³ These figures underscore the importance of looking for compromised adrenocortical status in patients admitted to a critical care unit leading to chronic adrenal insufficiency.

Clinical Features of Acute Adrenal Insufficiency

The clinical presentation of acute adrenal insufficiency may vary from one of unexplained fever with extreme lassitude, abdominal pain and nausea to that of severe hypovolemic shock with hypotension unresponsive to intravenous saline infusion and vasopressors.

Detailed history and further clinical evaluation will bring out the cause of the adrenal crisis and the type. The tell tale pigmentation of Addison's disease with a recent history of one of the precipitating factors - an intercurrent medical, surgical or traumatic illness will point to a primary type of Addisonian Crisis. A past history of having been on long-term steroid therapy, which had been withdrawn recently, will lead to a diagnosis of HPA axis dysfunction. Secondary type of acute insufficiency will also be apparent if there is a past history of having been treated for a pituitary tumor or a catastrophic history of sudden severe headache with visual defect and perhaps paralysis of III, IV and VI cranial nerves suggestive of pituitary apoplexy. Similarly a history of postpartum hemorrhage will suggest a Sheehan's syndrome with acute adrenal crisis.

Diagnosis

After an emergency clinical evaluation one proceeds to confirm the diagnosis but not before initiating therapeutic measures like rapid replacement of intravenous fluids with NaCl and dextrose. A bolus dose of 20 mg dexamethasone is also given intravenously - this will not

influence the plasma cortisol assay unlike hydrocortisone, prednisolone or methyl-prednisolone. A random plasma cortisol assay is carried out and a level of less than 18 µg/dl during a stressful clinical situation implies deficient cortisol production.

Once the patient's condition is stabilized a confirmatory provocative test using synthetic ACTH needs to be carried out. A low dose synacthen test using 1µg intravenously and measuring plasma cortisol 30 minutes and 60 minutes later is preferred to traditional high dose synacthen (250 µg) test. Adrenal function is considered normal if either basal or post-injection plasma cortisol level is 20 µg/dl or more.² In case the short synacthen test is normal and primary adrenal failure is excluded one proceeds to do a plasma ACTH estimation if facilities are available. Development of an IRMA assay for ACTH has simplified considerably the differential diagnosis of adrenal insufficiency.¹⁷ The test is simple, reliable, inexpensive and can be done as an outpatient procedure. A low or normal ACTH in the face of a low basal plasma cortisol clinches the diagnosis of secondary adrenal failure due to either a dysfunction of hypothalamus or pituitary or a significant suppression of HPA axis. Conversely an elevated ACTH in a patient with adrenal insufficiency suggests primary adrenal disease.

Insulin tolerance test where insulin induced hypoglycemia is used to test the integrity of the HPA axis by measuring the plasma cortisol is an alternative if ACTH assay is not available. An IV bolus of 0.15 units/kg of regular insulin is given and blood sugar and cortisol are measured every 15 minutes for the next one hour. The blood glucose should fall below 45 mg /dl to ensure adequate stimulation. The normal response is a plasma cortisol of more than 20 µg/ ml any time during the test. The test is uncomfortable, hazardous and has many false negatives and is no longer recommended by experts in the field.¹⁸

Metyrapone, a competitive inhibitor of 11 dehydroxylase enzyme involved in the synthesis of cortisol has been employed to document the integrity of HPA axis. It, however, has many drawbacks and had not been found useful in the differential diagnosis of adrenal insufficiency.³

Additional Investigations

Apart from the hormonal evaluation additional tests are necessary to identify the etiology and the precipitating event and to assess the associated abnormalities which will have to be taken into account in planning the therapeutic strategy.

A. Laboratory studies:

- (i) *Biochemistry*: Electrolytes including bicarbonates
- Plasma glucose, BUN and creatinine, calcium
 - Arterial blood gas

In one series hypoglycemia was present in 67%, hyponatremia in 88%, hyperkalemia in 64% and hypocalcemia in 6-33%.¹⁹

(ii) *Blood count may indicate several abnormalities*:

- Anemia normocytic normochromia – due to chronic disease or macrocytic due to associated autoimmune disease
- Neutrophilia – if bacterial infection is the precipitating cause
- Eosinophilia is usual finding
- Lymphopenia in HIV and other viral infections
- Elevated ESR/CRP as evidence of ongoing inflammation/infection

(iii) Thyroid function test, serum vitamin B₁₂ estimation, PTH if MEA is suspected.

(iv) *Cultures*: Blood and others in view of the fact that infection is one of the important precipitating causes.

(v) Serological and immunological tests for HIV and opportunistic infections.

B. *Imaging*

- *Chest radiography*: Tuberculosis, Histoplasmosis, carcinoma lung, sarcoidosis, lymphoma
- CT scanning/MRI:

- *Abdomen Adrenal*: Hemorrhage/ infiltration/atrophy/enlargement/ metastasis
- *Brain*: Pituitary/hypothalamus/stalk for primary or secondary neoplasm/ infarction/Hemorrhage/Craniopharyngiomas

C. *Histopathology / Cytology*:

- Adrenals/Lymph nodes

Summarizing the diagnostic evaluation of suspected acute adrenal insufficiency should include a rapid appraisal of present and past history, a quick but thorough general and systemic examination and an urgent laboratory work-up side by side with emergent supportive measures.

Management of Addisonian Crisis

Addisonian crisis is a life-threatening event requiring astute clinical suspicion, emergency work-up and aggressive therapeutic measures - the last two to proceed simultaneously. The patient will necessarily be in a ICU setting. After obtaining a blood sample for a random plasma cortisol, electrolytes, blood glucose, blood counts and culture, a rapid infusion of dextrose-saline is setup with measurement of CVP in elderly and those with known cardiovascular disease. 100 mg of hydrocortisone is injected intravenously and vasopressors are started if hypotension persists. Hydrocortisone is repeated in the same dose every six hours till the condition stabilizes in 24-48 hours and then the dosage is gradually reduced to 100 mg every eight hours for the next 48 hours and then changed to oral replacements once the diagnosis is confirmed.

On the other hand, if the diagnosis is uncertain and if a proper hormonal evaluation with early morning and midnight levels of plasma cortisol followed by dynamic tests are required intravenous dexamethasone 20 mg is given on first day followed by 10 mg daily till the diagnosis is confirmed or excluded (dexamethasone does not interfere with cortisol assays).

Over the next two to three days once the patient's condition stabilizes, other investigations aimed at arriving at the type of acute adrenal insufficiency and etiological diagnosis are undertaken, as also the workup to identify any precipitating cause which need to be treated. Empiric antibiotics are indicated if infection is suspected till the culture reports come in and if there is evidence of coagulopathy, fresh frozen plasma will be indicated.

Once the crisis is over and the patient is ambulant with amelioration of fatigue and regaining of appetite with normalization of blood pressure, electrolytes and blood sugars he is to be put on life-long replacement therapy consisting of oral hydrocortisone in physiological dosages. The daily production of cortisol is approximately 8 mg/m²/day.³ Based on this the daily replacement dose of hydrocortisone has now been recommended to be not more than 15-25 mg/day - much lower than the earlier recommended dose of 30 mg/day. It is given in split dosages - either 5 mg thrice daily or 10 mg in the morning and 5 mg once or twice daily later as required. In secondary adrenocortical insufficiency mineralocorticoid supplement is not indicated but in primary adrenal disease, fludrocortisone 0.1-0.2 mg is given once daily if hyponatremia and orthostatic hypotension persist.

Patient education is mandatory as part of continued surveillance. He should carry an 'Alert Card' indicating the nature of illness and the dosage of cortisol with clear instructions to double the dose in case of minor illness but increase it to 3-4 times in case of severe illness, trauma, cardiovascular event and peri-operatively.²⁰

PREVENTION OF ACUTE ADRENAL CRISIS

Corticosteroids are a standard treatment in many disease states with an inflammatory Etiology and are also being used empirically whenever the diagnosis is unclear, leading to suppression of HPA axis. This suppression can occur even with short courses of 5-7 days and recovery may take upto five days.²¹ Longer courses and higher dosage cause chronic suppression which may take

upto one year for recovery.²² This suppression occurs with both oral and intravenous administration and to a lesser extent even with prolonged inhaled intranasal or topical routes. It is, therefore, important to elicit such a history anytime in the past as also to find out if the person is on replacement therapy. This is mandatory in any person slated to undergo surgery or pregnancy or in case he is admitted with any intercurrent illness including trauma. Table 2 briefly outlines some guidelines for adrenal supplementation in such patients.²³

CONCLUSION

Addisonian crisis is a medical emergency often missed as it is not thought of. One needs to be fully conversant with the varied clinical setting and its presentation and need to exclude the possibility in all cases presenting with unexplained hypovolemic shock. A history suggestive of a chronic adrenocortical insufficiency either due to a primary adrenal disease or secondary due to pituitary or suppressed hypothalamic – pituitary function due to steroid therapy would help as also the identification of a precipitating factor like infection, surgery or trauma. One of course should also be aware of the catastrophic presentation due to pituitary apoplexy or adrenal hemorrhage. In India, apart from the tubercular infection of the adrenals with chronic insufficiency occasionally presenting with adrenal crisis due to intercurrent illness, one other condition that has to be considered is HIV which can cause adrenal insufficiency in several ways. The importance of early diagnosis and prompt institution of therapy – which involves correction of the hormones, fluid and electrolyte deficiency is to be stressed as also the long-term follow up of such patients with compromised adrenal functions. In no other medical emergency rapid institution of corrective therapy are the results more dramatic or rewarding.

REFERENCES

1. Oelkers W. Adrenal Insufficiency. *N. Engl J Med* 1996;335:1206-12.
2. Torrey SP. Recognition and management of Adrenal Emergencies. *Emergency Medicine Clin N America* 2005;23.
3. Bouillon R. Acute Adrenal Insufficiency. *Endocrine Metab Clin N Am* 2006;35:767-75.
4. Bhatia E. A profile of Addison Disease as seen in a referral centre in North India. Proceeding of 35th Annual conference of Endocrine Society of India, 2005, New Delhi.
5. Arlt W, Allolio B. Adrenal Insufficiency. *Lancet* 2003;361:1883-93.
6. Grinspoon SK, Bilezikian JP. HIV disease and the endocrine system. *N Engl J Med* 1992; 327:1360-65.
7. Marik P, Kiminyo K, Zaloga G. Adrenal insufficiency in critical ill patients with human immunodeficiency virus. *Crit Care Med* 2002;30:1267-73.
8. Eledrisi M, Verghese A. Adrenal insufficiency in HIV infection: A review and recommendations. *Am J Med Sci* 2001;321:137-44.
9. Piedrola G, Casado J, Lopez E. Clinical features of adrenal insufficiency in patients with acquired immunodeficiency syndrome. *Clin Endocrin* 1996;45:97-101.
10. Varon J, Chen K, Stanbach G, Rupert Waterhouse, Carl Friderichsen. Adrenal apoplexy. *J Emerg Med* 1998;16:643-47.
11. Johri S, Gorthi SP, Anand AC. Meningococcal meningitis. *MJAFI* 2005;61:369-74.
12. Hamilton D, Harris M, Foweraka J. Waterhouse-Friderichsen as a result of non meningococcal infection. *J Clin Pathol* 2004;57:208-29.
13. Vella A, Nippoldt T, Morris J. Adrenal haemorrhage : A 25 years experience at the Mayo Clin Proc 2001;76:161-68.
14. Satta M, Corsello S, Della Casa S. Adrenal insufficiency as the first clinical manifestation of the primary antiphospholipid antibody syndrome. *Clin Endocrin* 2000;52:123-26.
15. Biousse V, Newman NJ, Oyesiku NM. Precipitating factors in pituitary apoplexy. *J Neurol Neurosurg Psychiatry* 2001;71:542-45.
16. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;288:862-71.
17. Loriaux DL, Mc Donald WJ. In adrenal insufficiency. *Textbook of Endocrinology*. Degroot LJ, Jamesoe JL 4th (Ed). 2001. WB Saunders, Philadelphia.
18. Plumpton FS, Besser GM. The adrenocortical response to surgery and insulin induced hypoglycaemia in corticosteroid treated and normal subjects. *Brit J Surg* 1969; 56 : 216-22.
19. Klauer K. Adrenal insufficiency and adrenal crisis. *Emergency Medicine, Mass Gen Hosp* 2007 Abstract.
20. Jacoloi J Corticosteroid replacement in critically ill patients. *Crit Care Clin* 2006; 22:245-53.

21. Streck W F, Lockwood DW. Pituitary adrenal recovery following short term suppression with corticosteroids. *Am J Med* 1979; 66:910-14.
22. Lamberts SWJ, Bruining HA, DeJong FH. Corticosteroid therapy in severe illness. *New Eng J Med* 1997; 337: 1285-92.
23. Coursin DB, Wood KE. Corticosteroid Supple-mentation for adrenal insufficiency. *JAMA* 2002; 287:236-40.

MULTIPLE CHOICE QUESTIONS

1. **The commonest cause of adrenal deficiency in India is:**
 - A. Autoimmune adrenalitis
 - B. 21-hydroxylase deficiency
 - C. Tubercular infection
 - D. Chronic meningococcal septicemia
 2. **Adrenal hemorrhage or infarction leading to acute adrenal insufficiency can occur in:**
 - A. Meningococcal septicemia
 - B. Antiphospholipid antibody syndrome
 - C. Heparin induced thrombocytopenia (HIT)
 - D. All of the above
 3. **Acute HPA axis deficiency is commonly due to :**
 - A. Hypothalamic disease
 - B. Autoimmune hypophysitis
 - C. Pituitary apoplexy
 - D. Empty sella syndrome
 4. **The commonest cause of acute secondary adrenocortical insufficiency:**
 - A. Sheehan's syndrome
 - B. Head injury
 - C. Abrupt withdrawal of steroid therapy
 - D. Basal meningitis
 5. **In the diagnosis of acute adrenal insufficiency:**
 - A. Plasma cortisol assay is diagnostic
 - B. Short synacthen test with plasma cortisol estimation after 30 and 60 minutes is preferred
 - C. Insulin hypoglycemia test is mandatory
 - D. Metyrapone test is always indicated
 6. **In the management of Addisonian crisis:**
 - A. Normal saline infusion is preferred to glucose saline infusion
 - B. Intravenous hydrocortisone in massive doses will be required
 - C. Fludrocortisone is essential for emergency treatment
 - D. After emergency treatment, daily requirement of hydrocortisone is around 40 - 60 mg.
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1. C 2. D 3. C 4. C 5. B 6. B