Endotext

ADRENAL DISORDERS IN THE TROPICS

Pradip Mukhopadhyay MD, DM. Professor, Department of Endocrinology, Institute of Post Graduate Medical Education & Research, Kolkata, India. pradip.mukherjee@gmail.com
Kaushik Pandit MD, DM, FRCP, FACE, Honorary Scientific Officer, Department of Endocrinology. Institute of Post Graduate Medical Education & Research, Kolkata, India. kpandit3@gmail.com
Sujoy Ghosh MD, DM, FRCP, FACE, Professor, Department of Endocrinology. Institute of Post Graduate Medical Education & Research, Kolkata, India. drsujoyghosh2000@gmail.com

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ABSTRACT

The adrenal gland in conjunction with the pituitary gland is one of the major components of the endocrine system and regulates blood volume, blood pressure, serum electrolytes, and stress responses. Dysfunction of the adrenal glands may be related to diseases of the adrenal glands or pituitary gland. Adrenal disorders may present either due to structural or functional abnormalities. In the tropical countries, adrenal insufficiency is primarily due to adrenal infection by tuberculosis, adrenal mycosis infections, and adrenal hemorrhages. HIV (Human immunodeficiency virus) related adrenal problems are also common. Adrenal dysfunction due to pituitary disorders still occur frequently in tropical region and include Sheehan's syndrome, vasculotoxic snake bite, and thalassemia. Adrenal hormone excess typically occurs secondary to exogenous glucocorticoid use. Adrenal disorders that occur in the developed world occur with similar frequencies in tropical regions.

INTRODUCTION

Adrenal glands are one of the major peripheral organs necessary for homeostasis including maintenance of blood volume, blood pressure, and serum electrolytes. Disorders of adrenal glands are common in clinical practice. Adrenal dysfunction in tropical countries often occurs due to specific etiologies that differ from the typical causes of adrenal dysfunctions that commonly occur in other parts of the world (Table 1).

Table 1. Classification of Adrenal Disease in the Tropics

Adrenal insufficiency:

1. Primary:
    1) Adrenal Tuberculosis
    2) Adrenal Mycosis
    3) Adrenal Haemorrhage
2. Secondary:
    1) Sheehan's Syndrome
    2) Vasculotoxic Snake Bite
    3) Thalassemia's
3. Both Primary and Secondary:
    1) HIV

Adrenal Hormone excess syndromes:

1. Exogenous Glucocorticoid hormone excess syndromes
2. Licorice induced syndrome of apparent mineralocorticoid excess

PRIMARY ADRENAL INSUFFICIENCY

The causes of primary adrenal insufficiency that are more frequent in tropical regions include infection of the adrenal glands by tuberculosis or mycotic infections. In addition, autoimmune Addison's disease or adrenal failure as a component of polyglandular syndromes are equally prevalent in tropical regions as is in other parts of the world.

Adrenal Gland Tuberculosis

Adrenal gland tuberculosis or Tuberculous adrenalitis is the result of infection of adrenal gland by mycobacterium tuberculosis. The infection causes a destructive lesion of the adrenal cortex with uncertain chances of recovery and remains one of the most important causes of Addison's disease in the tropical countries (1). In fact, the adrenal glands are the most common endocrine organs to be involved in tuberculosis (2). Adrenal gland tuberculosis occurs almost always secondarily due to the hematogenous spread of the bacilli to the gland with the primary focus in lung. Adrenal failure or Addison's disease clinically manifest when at least 90% of the gland has been destroyed (1,2,3). Though classically the adrenal cortex is involved, the medulla also may be involved in many cases of adrenal tuberculosis (3,4).

PATHOPHYSIOLOGY

It is interesting to know why the adrenal glands are susceptible to infections. In fact, adrenal gland infections are common in response to a distant infection elsewhere in the body and in disseminated infection. Autopsy examination revealed that the prevalence of adrenal tuberculosis is about 6% in patients with active tuberculosis (4). However, subclinical adrenal dysfunction may be present in about 60-70% of patients with active tuberculosis (5). In any of these situations, there is an exaggerated response of the hypothalamo-pituitary-adrenal axis to produce excess cortisol in response to the stress of infection. This stress induced hypercortisolemia shifts the balance in the Th1/Th2 cell ratio towards a Th2 response (6). This T cell dysfunction (which is primarily responsible for cell mediated immunity) and low DHEA levels increases the host susceptibility to infection to mycobacterium tuberculosis and other organisms (6). Low DHEAS levels have been documented in tuberculosis (1,6). In addition, endotoxin released in response to the hyperactive HPA axis can cause pathological changes in the adrenal glands to increase the susceptibility to infection (7). The intrinsically rich vascularity of the adrenal glands promotes all of these pathophysiological events.

Histopathologically, four classic patterns have been described in adrenal tuberculosis (3). These are: granuloma (caseating or non-caseating), enlargement of the gland with destruction by inflammatory granuloma, mass lesions due to cold abscesses, and adrenal atrophy due to fibrosis related to chronic infection. Caseating granuloma is the commonest one and this is identified in about 70% of cases (4). However, granuloma with typical presence of Langhan's giant cell are less common and identified in less than 50% of cases (4), probably due to anti-inflammatory effects of local glucocorticoids. Calcification of the gland is a common but it is present in other chronic infections of the adrenal glands (3). In about 25 % cases the infection may be unilateral (1).

PRESENTATION

Typical symptoms of adrenal gland tuberculosis in a patient with diagnosed tuberculosis (whether or not on anti-tubercular chemotherapy) are mucocutaneous pigmentation in association with chronic ill health, vomiting, postural hypotension, and anorexia (3). The features are similar to Addison's disease due to other conditions. As the features of progressively evolving adrenal hypofunction are mostly nonspecific, a high index of suspicion is necessary in subjects with diagnosed active tuberculosis especially when pigmentation is absent. However clinical manifestations may take months to years to become apparent.

The patient may also present rarely with frank adrenal crisis with hypotension, hyponatremia, hyperkalemia, and low serum cortisol levels. The crisis may even be precipitated after administration of rifampicin which increases the hepatic metabolism of

cortisol in the background of subclinical adrenal dysfunction (8).

Adrenal tuberculosis may also present as an adrenal incidentaloma. Nonspecific abdominal pain, weight loss, dizziness, and vomiting may lead to imaging of the abdomen which may reveal an incidental adrenal mass often with calcification. The differential diagnosis of Addison's disease with adrenal enlargement includes (apart from tuberculosis) malignancy, fungal infections, hemorrhage, amyloidosis, sarcoidosis, etc. (3).

Subclinical adrenal dysfunction is also very common and should be actively sought in all cases of active tuberculosis (5).

INVESTIGATIONS

Laboratory Studies

Common laboratory findings include anemia, hyponatremia, and hyperkalemia. In the presence of a positive Mantoux test in association with typical clinical manifestations of adrenal hypofunction, adrenal tuberculosis must be ruled out. Adrenal insufficiency should be ruled out by using a standard protocol. Serum cortisol levels <5 µg/dL and a plasma ACTH more than 2-fold the upper limit of the reference range is suggestive of primary adrenal insufficiency (9). The serum cortisol may remain in the low-normal to mid-normal range in many cases. However, a standard dose (250 µg) intravenous cosyntropin (Synacthen) stimulation test establishes the diagnosis of adrenal insufficiency when the peak level of cortisol remains below 18 µg/d (9). Random cortisol levels, though useful during an acute crisis, is not usually sufficient to rule out adrenal insufficiency (9). Documentation of subclinical adrenal dysfunction may reveal mineralocorticoid deficiency alone (as demonstrated by raised plasma rennin activity) when stimulated cortisol is within the normal range (8).

Imaging of Adrenal Glands

CT scan of the abdomen is the most important non-invasive investigation with a very good spatial resolution to diagnose adrenal tuberculosis. The findings are usually bilateral and vary with the duration of the disease before diagnosis (1, 3). The most common early findings during the initial 2 years include a mass lesion with smooth adrenal contour preserved. The glands may show central or patchy hypodensity corresponding to areas of caseous necrosis (3). On contrast administration there is peripheral rim enhancement. Calcification is not a common feature in early tuberculosis (3).

With chronic infection, the adrenal glands become small and shrunken, often with associated calcifications and the margins become irregular (3). Though prevalence and intensity of calcification increases with the duration of tuberculosis, this is not a specific finding and may be associated with other conditions.

Though MRI is also done in many cases, this imaging modality has limitations to assess calcification. However, T1 weighted image shows hypointense or isointense areas and T2 weighted image shows hyperintense areas because of necrosis (3).

Percutaneous FNA/ TB PCR

For confirmation of adrenal tuberculosis tissue diagnosis is required. CT scan guided fine needle aspiration from the adrenal gland is necessary to obtain adequate tissue specimens (3, 10). Pathological and microbiological confirmation is necessary, especially where there is isolated adrenal involvement. However, it should be remembered that PCR and culture of these specimens for tuberculosis bacilli are not consistently positive (3). Hence a combination of histopathology, PCR, and culture may be necessary to confirm the diagnosis (3). However, routine search for pulmonary tuberculosis with necessary investigations is mandatory.

TREATMENT

Treatment of adrenal insufficiency in tuberculosis requires administration of both glucocorticoids and mineralocorticoids. As the medulla is frequently involved, patients may require higher doses for maintenance of blood pressure. At the same time, rifampicin used in the anti-tubercular regimen is a potent hepatic enzyme inducer and accelerates cortisol metabolism. This also may necessitate a higher dose of glucocorticoids for adequate treatment. However, aldosterone is less likely to be

involved. Adrenal crisis is also reported to occur following the administration of rifampicin (11).

Therapy is monitored with blood pressure, body weight, well-being, serum electrolytes and blood glucose. Patients should be also be monitored for over treatment with glucocorticoids with weight gain, blood pressure, decreasing bone mineral density, and other manifestations of Cushing's syndrome. All subjects should carry a 'steroid card' and should be advised strictly on how to increase the dose of glucocorticoid in stressful situations such as fever, infection, vomiting, trauma, etc.

PROGNOSIS FOR ADRENAL FUNCTION RECOVERY

Chances of adrenal recovery with anti-tuberculosis therapy are uncertain and unpredictable. When the disease is diagnosed late, the glandular destruction is usually significant and the gland becomes atrophic, and anti-tuberculosis therapy does not lead to a recovery of adrenal function (12, 13). If therapy is started early before the gland is destroyed recovery may occur (14, 15). It is also suggested that if the gland size remains the same on subsequent follow up CT scans, it is prudent to follow up the patient for adrenal function recovery.

Adrenal Mycosis

HISTOPLASMOSIS

Adrenal Histoplasmosis caused by the dimorphic fungus Histoplasma capsulatum, is a recognized cause of adrenal insufficiency. Though this opportunistic pathogen is known to affect immunocompromised individuals predominantly (16), it can rarely infect immunocompetent individuals (16, 17). This is the most fungal infection of the adrenal glands (16, 18).

Involvement of the adrenals can occur during disseminated infection or many years after disease resolution (18). Adrenal involvement can vary from an asymptomatic milder form to a very severe form that presents with extensive bilateral granulomatous involvement of the entire adrenal gland with calcified lesions culminating in acute adrenal insufficiency (18, 19). Rarely the involvement can be unilateral (17). The common differential diagnosis includes tuberculosis, other fungal infections, adrenal metastasis, primary adrenal malignancy, and primary adrenal lymphoma (16). In immunocompetent individuals it commonly presents with a unilateral or bilateral adrenal mass with constitutional symptoms.

The hypothesis for why histoplasmosis involves the adrenal glands with increased frequency includes the local high levels of glucocorticoids in association with a relative paucity of reticulo-endothelial cells within the adrenal gland (6). The gland is destroyed by direct infection that leads to local ischemia and infarction due to perivasculitis, and caseation (6).

Diagnosis depends on imaging studies with pathological confirmation. CT scan of the adrenal glands typically reveals symmetric enlargement with central hypodensity and characteristic peripheral rim like enhancement (20). Frequently calcification is also present, particularly during the healing phase (20). Percutaneous ultrasound or CT guided fine-needle aspiration or biopsy is necessary for tissue diagnosis (18). The characteristic cytopathological findings are the presence of numerous small oval yeast like structures inside the cytoplasm of macrophages (16). On a necrotic background, this yeast like structures inside the macrophages is surrounded by a clear ring of space resembling a capsule. However, the gold standard for diagnosis is documentation of the organism in the culture of pathological specimen (16). Bhansali et al reported a high uptake in adrenal glands in FDG-PET scan in patients with adrenal histoplasmosis (17).

Treatment for adrenal histoplasmosis depends on the severity of the infection and the condition of the patient. For severe infection in critically ill patient's amphotericin B is used initially followed by long-term therapy with oral itraconazole (16). Parenteral liposomal amphotericin B is given 3mg/kg body weight for 2 weeks (17). The duration of therapy with itraconazole varies from six months to two years

depending on the patient's condition. For mild to-moderate histoplasmosis, the recommended treatment is itraconazole. The recommended dose is 200 mg twice daily given for 12 months (16). When itraconazole is used, liver enzymes should be monitored on a regular basis (18). Treatment for adrenal insufficiency follows the same principles as described earlier.

Though the remission rate from adrenal histoplasmosis is high with long-term oral itraconazole, adrenal insufficiency rarely resolves and reversal of adrenal dysfunction can be seen only in some patients after prolonged antifungal therapy (21). However, histoplasma in adrenals is reported to persist even 7 years after antifungal therapy (22).

OTHER FUNGAL INFECTIONS

Paracoccidioidomycosis Brasiliensis

Paracoccidioidomycosis brasiliensis is a dimorphic fungus and can cause chronic, progressive, suppurative and granulomatous disease which can lead to adrenal insufficiency (3). The disease is endemic in Latin America. Humans are the accidental host for the organism and females are rarely affected (23). Smoking and alcohol increase the risk. The lungs are the usual portals of entry. Juvenile forms of the disease are also known (23). Apart from frank adrenal crisis, it can present as progressive constitutional symptoms, hyperpigmentation, and low blood pressure with postural drop and bilateral adrenal enlargement in imaging studies with frank adrenal calcification detected by CT scans (24, 25). Histopathology with GMS stain shows multiple budding yeast with steering wheels appearance which is consistent with Paracoccidioides brasiliensis (24). However, confirmation of the organism by culture material is the gold standard for diagnosis. Serology for antibody detection is also useful in the diagnosis. Diagnosis and treatment of adrenal insufficiency is not different than described above for histoplasmosis. P. brasiliensis primarily causes adrenal destruction by embolic infection of small vessels by large fungal cells and granuloma formation (3). Subjects who receive early antifungals with itraconazole over a 1–2-year period may have a full recovery of adrenal function by preventing fungal embolism in adrenal gland vasculature and reducing ischemic necrotic destruction of the gland (3). Hence an early diagnosis is crucial for preventing the progression of adrenal dysfunction. However, persistence of high antibody titer against paracoccidioidomycosis at the end of treatment or during follow-up is a frequent finding in subjects with paracoccidioidomycosis.

Blastomyces Dermatitidis

Blastomyces dermatitidis is also a dimorphic fungus, which has a strong affinity for the adrenal gland for reasons described earlier. Overt adrenal insufficiency is less common and adrenal Blastomyces dermatitidis typically presents as bilateral adrenal incidentaloma during radiological investigations for other reasons (3). The portal of entry is through the lungs and when there is lymphohematogenous dissemination the disease spreads to other organs (26). In situations when it presents as adrenal insufficiency, the presentation, investigations, and management are similar to those described above. Diagnosis is by fine-needle aspiration guided by ultrasound or CT scan followed by cytologic and histologic examinations. However, the gold standard is fungal culture showing thick-walled, broad-based budding yeast cells (27). Treatment is with long term oral itraconazole. In patients with severe manifestations initial treatment with liposomal amphotericin B for 2 weeks could be used.

Cryptocoocus Neoformans

Cryptocoocus neoformans is an encapsulated yeast-like fungus which infects primarily immunodeficient hosts, particularly subjects infected with HIV or lymphohematogenous malignancies (28). In immunocompromised hosts it usually affects the central nervous system and lungs. However immune-competent individuals may also suffer adrenal cryptococcosis (29). Adrenal dysfunction is uncommon until almost the whole of adrenal gland is infiltrated with C. neoformans and caseating granulomas. Cryptococcosis is diagnosed by fine-needle aspiration biopsy of the adrenal mass. The serum cryptococcal antigen titer is highly elevated. Treatment is with antifungal therapy with fluconazole and amphotericin B. Adrenal enlargement by

Cryptococcus may be completely reversible without any abnormality after antifungal treatment (30). Cases not responsive to anti-fungal therapy have been reported to improve after unilateral or bilateral adrenalectomy (28, 29).

Miscellaneous

Pneumocystis jirovecii (previously known P. carinii) occurs in individuals with advanced HIV due to defects in cell mediated immunity. Spread to other organs including the adrenal glands is also possible (3). Adrenal failure associated with coccidioidomycosis and rarely candidiasis has also been reported.

Adrenal Hemorrhage; the Waterhouse Friderichsen Syndrome

This is a condition in which patient presents with acute hypotension and shock due to adrenal insufficiency arising from acute adrenal hemorrhage. The syndrome is typically related to infection with Neisseria meningitides infection (3). However, this is also known to occur in septicemia due to infections with Staphylococcus aureus, Streptococcus spp, Haemophilus influenzae, Corynebacterium diphtheria, etc. (3). Hence this is more common in the tropical region. The condition is hypothesized to be due to interplay between endotoxemia and elevated ACTH. The adrenal gland is anatomically prone to hemorrhage as it has three separate arterial supplies and does not have proportional venous drainage (3). In endotoxemia, elevated ACTH increases the blood supply several fold in this compromised anatomical setting. At the same time increased adrenaline secretion in relation to stress leads to constriction of adrenal veins, which further increases this imbalance between arterial supply and venous drainage. Management includes immediate fluid replacement and parenteral glucocorticoids apart from the management of the underlying infection.

SECONDARY ADRENAL INSUFFICIENCY

Adrenal insufficiency secondary to disorders of pituitary gland is also very common in developing countries in tropical regions. Secondary adrenal insufficiency caused by pituitary tumors and apoplexy, pituitary surgery, radiation therapy, hypophysitis, various genetic disorders, and withdrawal of exogenous steroids are equally common in tropical regions but certain other disorders like Sheehan's syndrome, thalassemia, and vasculotoxic snake bite induced pituitary failure are more common in tropical regions.

Sheehan's Syndrome

Sheehan's syndrome consists of various degrees of pituitary insufficiency, which develops as a result of ischemic pituitary necrosis due to severe postpartum hemorrhage. The important pathogenetic/predisposing factors include a small sella, increased pituitary volume, vasospasm induced by postpartum hemorrhage, thrombosis, and probable pituitary autoimmunity (31). In developed countries there has been a drastic reduction in the incidence of Sheehan's syndrome. This is primarily due to the remarkable improvement in obstetric care and availability of rapid blood transfusion. However, this remains as a major cause of hypopituitarism in the other parts of the world.

CLINICAL FEATURES

Most commonly the disorder presents as a lactation failure in the post-partum state and non-resumption of menses following child birth, which was complicated by massive post-partum hemorrhage leading to hypotension and shock. However, it may very rarely occur without massive bleeding or after normal delivery. Patients may present in the emergency with altered sensorium, loss of consciousness, seizure, shock, intractable vomiting, or more commonly with chronic complaints like asthenia and weakness, dizziness, anorexia, weight loss, nausea, and vomiting with a typical history of failure to resume menses and lactation failure following child birth (31). Apart from anterior pituitary hormone deficiency, symptoms like anemia, pancytopenia, osteoporosis, cognitive impairment, and poor quality of life are also present in these patients (31,32). Very rarely diabetes insipidus may occur. However, the mean age of the participants may be as late as 40 years or more and the mean

interval between inciting event to diagnosis may be as high as 10 years or more (33).

Adrenal insufficiency due to ACTH deficiency is reported to occur in up to 100% of cases (in fact deficiency of all anterior pituitary hormones occur in a variable percentage of patients and may be up to 100%) (32). Weakness, fatigue, and postural drop are common manifestations. Hyponatremia is particularly common in Sheehan's syndrome, which may be due to glucocorticoids deficiency coupled with increased AVP release as a consequence of reduced blood pressure and cardiac output resulting from glucocorticoid deficiency (32).

DIAGNOSIS

The basal pituitary hormonal levels and those after dynamic tests are beyond the purview of this chapter. However adrenal insufficiency is diagnosed with a morning cortisol level of 3 mcg/dl with low or inappropriately normal ACTH or a cosyntropin stimulated cortisol level <18 mcg/dl. Documentation of growth hormone deficiency does not require a dynamic test in presence of other pituitary hormone deficiencies. Only low age specific and assay specific IGF-1 assay may be sufficient to document adult growth hormone deficiency (AGHD) (34).

The preferred radiological imaging is an MRI of hypothalamic pituitary area. CT scan may also be helpful. MRI findings in Sheehan's syndrome usually vary with the stages of the disease. In earlier stages of the disease there may be an enlarged pituitary gland with central hypodensity (suggestive of infarction). However, an empty sella (complete or partial) is considered to be a characteristic of Sheehan's syndrome in established cases (32).

TREATMENT

The acute adrenal crisis in Sheehan's syndrome is treated with intravenous glucocorticoids. In other patients' glucocorticoids should be started orally with hydrocortisone 15-25 mg daily in 2-3 divided doses with the higher dose in the morning and a lower dose in the evening (35). Mineralocorticoids are not necessary in general (35). Once daily prednisolone may also be used at a dose of 2.5-5 mg once daily in the early morning. As GH deficiency decreases cortisol clearance, it may necessary to increase the dose of glucocorticoid for those who receive GH treatment (35). Therapy is monitored with blood pressure, body weight, well-being, serum electrolytes, and blood glucose. Patients should be also be monitored for an overdose of glucocorticoids with weight gain, blood pressure, decreased bone mineral density, and other symptoms and signs of Cushing's syndrome. All subjects with Sheehan's syndrome should carry a 'steroid card' and should be advised strictly on how to increase the dose of glucocorticoid in stressful situation such as fever, infection, vomiting, trauma, etc.

Subjects with Sheehan's syndrome should also be treated with levothyroxine, combined oral contraceptives according to guideline, calcium and vitamin D supplements, and growth hormone therapy (if possible) according to the protocol of adult growth hormone deficiency.

Viscerotropic Snake Bite

Snakebite is a major public health problem in tropical regions and is considered as one of the most neglected tropical diseases. The development of a Sheehan-like syndrome with chronic hypopituitarism following Russell viper envenomation is fairly common. Hypoadrenalism due to ACTH deficiency is the commonest abnormality (36). However acute hypopituitarism with predominant glucocorticoids deficiency has also been reported (37).

The venom of vipers is vasculotoxic in nature and the clinical features of viper venomation include local cellulitis and tissue necrosis, bleeding manifestations, disseminated intravascular coagulation, shock, and acute kidney injury (AKI) (38). Hypopituitarism is particularly common following vasculotoxic snake bite in subjects who develop AKI requiring hemodialysis. Hypopituitarism can develop as early as 7 days following snake bites and should be evaluated for particularly in younger subjects, especially those requiring increasing number of sessions of hemodialysis and in subjects with abnormal 20 min WBCT (whole blood clotting test) at presentation

(36,39). On the other hand, the time of onset/presentation of hypopituitarism following snake bite may be as long as up to 24 years (40). Acute hypopituitarism is thought to occur due to acute damage to the pituitary gland at the time of the precipitating event, but a gradual/slower progression of pituitary damage may occur over years due to other unknown mechanisms (36).

Those who survive acute snake bite may later present with altered sensorium, loss of consciousness, seizure, shock, intractable vomiting, or more commonly with chronic complaints like asthenia and weakness, dizziness, anorexia, weight loss, nausea, vomiting and amenorrhea in females (36).

Variable degrees of hypopituitarism may be present. Cortisol deficiency is reported to be the commonest abnormality. Secondary adrenal insufficiency is diagnosed with a morning cortisol level of 3 mcg/dl with low or inappropriately normal ACTH or a co-syntropin stimulated cortisol level <18 mcg/dl (36). Documentation of growth hormone deficiency is done as mentioned in section of Sheehan's Syndrome (34).

The preferred radiological imaging is the MRI of hypothalamic pituitary area which may show partial or complete empty sella or evidences of old hemorrhage. However, these changes are not present in all cases (41).

Treatment of secondary adrenal insufficiency and other hormone deficiencies are similar to described above. All subjects with hypopituitarism on glucocorticoids supplements should carry a 'steroid card' and should be advised on how to increase the dose of glucocorticoid in stressful situation such as fever, infection, vomiting, trauma, etc.

Thalassemia Major

Thalassemia's are inherited autosomal recessive disorders of hemoglobin synthesis. Thalassemia major is the most severe form of beta thalassemia which involves the beta chain of hemoglobin. Organ dysfunction in thalassemia is principally attributed to excessive iron overload and suboptimal chelation. The precise underlying mechanism of iron overload induced organ dysfunction is not very unclear. The current management of thalassemia includes regular transfusion programs and chelation therapy. Pre-marital counselling and assessment with HPLC to assess the asymptomatic carrier has reduced its prevalence significantly in the developed world. However, this is still a major problem in many parts of the world. Prevalence of adrenal insufficiency is variable and depends on the severity of iron overload. This secondary hemochromatosis can disrupt adrenal function by affecting the hypothalamic-pituitary-adrenal axis at the hypothalamic or pituitary level (42). In more severe cases primary adrenal failure may supervene due to iron deposition in the adrenal glands (42). Additionally, an extramedullary hematopoietic tumor has been reported in HbE thalassemia and beta thalassemia as non-hormone secretory unilateral or bilateral adrenal enlargement resembling adrenal myelolipoma (43).

Biochemical adrenal insufficiency is reported to occur from 0% to 45% of subjects with thalassemia major (42), but adrenal crisis or clinical adrenal insufficiency is extremely uncommon and mostly they are asymptomatic. However, subclinical cortisol deficiency is not uncommon. In this context it should be remembered that mild symptoms of adrenal insufficiency like asthenia, weight loss, or postural drops are frequently overlooked as these features are common in thalassemia subjects with low levels of hemoglobin (42).

The unique finding in subjects with thalassemia is the dissociation between adrenal androgen levels with cortisol and aldosterone levels. This paradox is reflected by frequent documentation of low serum DHEA, DHEA-sulfate, androstenedione, and testosterone levels in the presence of normal serum cortisol and aldosterone levels (44). Absence of adrenarche occurring in most adolescents with thalassemia major is probably explained by this phenomenon (45).

Diagnosis of adrenal dysfunction in thalassemia is similar to other causes of secondary adrenal insufficiency. If the morning cortisol is not unequivocally low, synacthen stimulation test should

be done with either the low dose (1 µg) or the standard high dose (250 µg). A peak cortisol level of >18 µg/dL after 30-60 min of intravenous synacthen excludes adrenal insufficiency. Alternately an insulin tolerance test with a similar cut-off may also be done. Treatment of clinical adrenal insufficiency is similar to that described above. Subjects with subclinical adrenal insufficiency require only steroid coverage during periods of stress.

HIV AND ADRENAL DYSFUNCTION

Endocrine manifestations of HIV infection may include adrenal dysfunction, hypothyroidism, hypogonadism, insulin resistance and diabetes etc. Changes in the HPA (hypothalamic-pituitary-adrenal) axis are the most frequent abnormality (46). Adrenal dysfunction in HIV infection may be a consequence of concomitant systemic illness, opportunistic infections, and neoplasm (47).

Probably the most frequent adrenal abnormality is a stress induced elevation in serum cortisol and ACTH (46). This may be due to activation of the HPA axis due to HIV infection itself or pro-inflammatory cytokines (e.g., IL-1β, IL-6 and TNF-α) (46). Alternately a peripheral increase in the conversion of cortisone to cortisol due to activation of 11-β HSD type 1 in adipose tissue or decrease in cortisol metabolism may be responsible for increased cortisol with subnormal ACTH (46). Tissue hypersensitivity to glucocorticoids is also reported in subjects with HIV-1 infection, which may result in hippocampal atrophy, altered secretion of cytokine/interleukins, etc. (48).

On the other hand, subclinical or clinical adrenal dysfunction can happen in about 10-20% of subjects with advanced disease and multiple co-morbidities when about 80-90% of the gland is destroyed (46). The involvement and destruction by HIV, opportunistic infections, or malignancies in the adrenal glands or the hypothalamus and/or pituitary area can result in either primary or secondary adrenal sufficiency (47).

The opportunistic infections include cytomegalovirus (CMV), Mycobacterium avium-intracellular and M. tuberculosis, fungal infections (such as Histoplasma, Cryptococcus, and Pneumocystis *jirovecii*), and Toxoplasma gondii (47). Of these opportunistic infections, CMV infection is known to be the commonest etiology with earlier literature reporting Cytomegalovirus adrenalitis in nearly 80 % of cases of HIV infection (46). However, due to improvements in active management of HIV by HAART (highly active anti- retroviral therapy), the prevalence of adrenal insufficiency has decreased over the last two decades.

Medications used for the treatment of HIV infection and its complication may also result in adrenal dysfunction. For example: Rifampicin used for mycobacterial infection is a known hepatic Cytochrome P 450 (CYP) enzyme inducer and can lower serum cortisol levels by enhanced cortisol metabolism. Ketoconazole used to treat severe mycotic infections inhibits adrenal steroid synthesis and can lead to glucocorticoid deficiency or even adrenal crisis in patients with impaired adrenal reserve (49). Interestingly, ART-related lipodystrophy (dorsocervical fat pad enlargement and visceral adiposity) may mimic Cushing's syndrome but it is typically not associated with hypercortisolism (49). On the contrary, some protease inhibitors (e.g., ritonavir) used in ART are reported to decrease metabolism of endogenous and exogenously co-administered glucocorticoids, resulting in an iatrogenic Cushing's syndrome.

Tumors of the adrenal gland in HIV infected patients include Kaposi's sarcoma and high-grade non-Hodgkin's lymphoma. Kaposi's sarcoma is secondary to co-infection with the oncogenic human herpes virus type 8 (HHV8) and non-Hodgkin's lymphoma could be secondary to Epstein-Barr virus (EBV).

Assessment for symptoms of adrenal involvement requires a high degree of suspicion as constitutional symptoms of HIV may mask the features of adrenal insufficiency. Morning serum cortisol should be done in all cases suspected for adrenal dysfunction. Stress induced hypercortisolemia does not require any further testing and low serum cortisol <5 µg/dl with an

elevated ACTH level requires treatment with glucocorticoids and mineralocorticoids. In other cases, synthacthen stimulated cortisol is used to determine the course of treatment. Stimulated cortisol <18 µg/dl, especially if associated with elevated plasma ACTH, should be treated as adrenal insufficiency. Asymptomatic subjects with stimulated serum cortisol <18 µg/dl should be advised to take stress doses of glucocorticoids only as mentioned before.

Diagnosis and management of adrenal disorders in a patient with HIV infection does not differ from that in immunocompetent persons in general.

ADRENAL HORMONE EXCESS SYNDROMES

Glucocorticoid Excess Syndromes

The primary cause of Cushing's syndrome, more common in tropical regions, is exogenous glucocorticoids. The background etiology for exogenous steroid usage includes: nephrotic syndrome, rheumatoid arthritis and other collagen vascular disease, bronchial asthma, Graves' orbitopathy, etc. Glucocorticoids used as inhalational agent for bronchial asthma, in creams and ointments for eczematous skin lesions may also be responsible. Endogenous steroid excess (Cushing's disease, ectopic ACTH syndromes, adrenal tumors) are equally common in tropical regions as in other areas of the world.

Often it is a challenge to suspect exogenous glucocorticoid use based on the patient's history, especially in situations when glucocorticoids were not being used for a therapeutic purpose. Subjects presenting with features suggestive of Cushing's syndrome should therefore mandatorily undergo testing for basal morning cortisol (with paired ACTH if possible) to rule out exogenous glucocorticoid use. A suppressed morning cortisol and plasma ACTH strongly suggests the diagnosis (50). One important caveat is that prednisolone may cross react with some cortisol assays giving false positive results in some chemiluminescent assay (51). Additionally, if the patient is receiving hydrocortisone, the result will also be fallacious to interpret. It is not uncommon in tropical regions that some form of glucocorticoids is being used in disguise as an alternative medicine for joint pain, respiratory problems, fever, or even as a weight gain therapy for young lean subjects. Hence a more detailed evaluation of the history with leading questions and scrutiny of all past records of medicine, including that of the alternative medicines, may sometimes reveal the offending agent.

The clinical features that suggest exogenous Cushing's syndrome are lack of pigmentation and the absence of hypertension and hirsutism (as exogenous Cushing's syndrome does not contain mineralocorticoids and androgens as opposed to endogenous Cushing's syndrome). Patients with exogenous Cushing's syndrome are prone to develop glaucoma, osteoporosis, psychiatric disturbances, etc. (50).

Once diagnosed, these subjects should be advised to withdraw the offending agents and should be given hydrocortisone in the lowest possible dose for preventing adrenal crisis. The withdrawal of hydrocortisone subsequently after 3 months depends on the morning cortisol, after stopping the previous evening dose and subjecting the patient to short synacthen test to assess the recovery of HPA axis. Those with morning cortisol between 5 -18 µ/dl should be advised stress coverage only. For bone protection, all subjects with exogenous Cushing's syndrome should receive bisphosphonate therapy unless contraindicated (52). Adequate calcium supplements with cholecalciferol should also be used.

For subjects receiving glucocorticoids for therapeutic purpose, it is essential to maintain bone protection, check for secondary diabetes and hypertension, and prevent gastric ulceration. Withdrawal (if at all possible) should be performed very slowly. When the therapeutic steroid reaches the lowest possible dose to prevent crisis, it is converted to equivalent dose of hydrocortisone and the same principle is used as described before.

Licorice Induced Syndrome Of Apparent Mineralocorticoid Excess

Licorice root extracts are used as a herbal medicine for several conditions like cough, peptic ulceration, etc. Licorice is also used as a sweetener and mouth freshener particularly in tropical regions (53). Licorice possesses some glucocorticoid activity, antiandrogen effect, estrogenic activity, and mineralocorticoid like activity. Subjects consuming excessive licorice may develop hypertension and hypokalemia (53). Sometimes this is severe enough to cause a cardiac arrhythmia. While screening for primary aldosteronism for subjects presenting with hypertension and hypokalemia, plasma aldosterone and plasma rennin activity are found to be suppressed in patients using licorice (53).

The active ingredient of liquorice is glycyrrhizic acid, which is hydrolyzed into glycyrrhetinic acid in vivo. Glycyrrhetinic acid has a very low affinity for the mineralocorticoid receptor but is a potent competitive inhibitor of the enzyme 11β-HSD type 2 which is preferentially expressed in kidney (54). Hence it may cause acquired 11β-HSD type 2 deficiency. The physiological role of the enzyme 11β-HSD type 2 is to inactivate cortisol to cortisone and thereby preventing access of cortisol to mineralocorticoid receptor. Cortisol and aldosterone have equipotent stimulating activity on mineralocorticoid receptor (54). Hence any situation associated with suppressed 11β-HSD type 2 activities may lead to overstimulation of mineralocorticoid receptors by cortisol, leading to hypertension with hypokalemia and metabolic alkalosis. After correction of hypokalemia, the screening test reveals suppressed aldosterone and plasma rennin activity (54). The hypertension is primarily due to sodium and water retention. A careful history for licorice ingestion clinches the diagnosis.

Treatment consists of avoidance of licorice products. In the interim period patients should be treated with oral potassium and spironolactone after the completion of screening of aldosterone rennin ratio (ARR). Withdrawal of licorice, even after prolonged use or ingestion of large amounts, leads to a complete resolution of the symptoms of acquired apparent mineralocorticoid excess (55).

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