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Adrenal Insufficiency Overview

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Abstract

Since Thomas Addison first reported adrenal insufficiency in the 19th century till nowadays still this entity shows challenging scenarios and recurrently reported as missed cases diagnosed retrograde after substantial delay. This is due to the wide variety and non-specific manifestations such as fatigue, malaise, loss of energy, loss of appetite and even occasionally present with mood disorders. Also there are exceptions for cardinal features of adrenal insufficiency such as absent pigmentation in secondary and some primary cases of Adrenal Insufficiency (A.I) and the cosyntropin test may give normal response if done early in secondary A.I. So in this article there is extensive literature review of the adrenal insufficiency covering a wide spectrum of areas starting from physiology back ground till the management lines and raising some important points such as the regenerative potential of the adrenal glands, the variety of presentations, the entity of pseudo-hypoadrenalism, some pitfalls in the diagnosis, possible self-recovery and management lines.

Keywords: Adrenal insufficiency; Cosyntropin test; Pseudo-hypoadrenalism

Physiology Background

The adrenal glands play a critical role for health, wellbeing and even for life. They act under control of other endocrine loops. The Hypothalamus-Pituitary-Adrenal Axis (HPA) and the Renin-Angiotensin-Aldosterone Loop (RAA). Each adrenal gland have a cortex and medulla, and the cortex has three zones.

The adrenal cortical zones and their secretion from out to inwards:

Zona Glomerulosa (ZG)

Secrete mineralocorticoids mainly aldosterone under control of the renin-angiotensin-aldosterone system. The Aldosterone acts on the kidneys-distal tubules and collecting ducts-to absorb sodium and secrete potassium so its role is crucial for maintaining intravascular volume and electrolyte balance.

Zona Fasciculata (ZF)

Secrete glucocorticoids mainly cortisol under higher control of the Hypothalamus-Pituitary axis.

Cortisol is a steroid hormone essential for life and its secretion shows circadian and pulsatile ultradian pattern [1]. Being steroid hormone it can cross the cell wall to act on cytoplasmic receptors which will transfer to the nucleus to exert its action. There are two forms: cortisone which is the inactive glucocorticoid circulating mainly in a free form with no significant diurnal variation and cortisol which is mostly protein bound with marked variability in the range of free cortisol level from 1 nmol/l at the lowest up to 100 nmol/l during peak times including stress [2].

Zona reticularis secretes the adrenal gonadal hormones in particular and adrenal androgens in females. Adrenal medulla secretes catecholamines. The Hypothalamus-Pituitary-Adrenal Axis (HPA) The pituitary gland is about 0.5-1 gm in weight located in the sella turcica and has two distinct parts anterior and posterior. About 20% of the anterior pituitary cells are corticotrophes responsible for ACTH secretion [3] under influence of the Corticotrophin Releasing Hormone (CRH) secreted from the hypothalamus. After its release the ACTH stimulates the zona fasciculata cells to secrete the glucocorticoids which would exert its action on several tissues including acting back on the hypothalamus-pituitary loop to suppress the CRH and ACTH in a very sensitive negative feedback mechanism.

Normally cortisol secretion shows significant circadian variation with the highest level early morning showing almost double the afternoon and evening levels and also secretion varies with age, weight, fat distribution and gender being higher in men than women, in old than young and with increased weight which is balanced by the increased urinary excretion (so it is not claimed to play role in body fat distribution in obese people) [4]. Action of glucocorticoids: Stress response, metabolic role (gluconeogenesis), plays role in maintaining vascular tone and immune regulation. So it is clear the crucial role of the adrenal glands through its major products glucocorticoids and mineralocorticoids as a gland essential for life and so hypoadrenalsim despite its rarity is really important to recognize as it is a life threatening condition.

With Pregnancy

During pregnancy one third of fetal cortisol comes from the maternal circulation but the other two thirds are secreted from the fetal adrenals that can be identified as early as 8 weeks gestation [1]. Pregnancy is associated with some endocrinologic changes including the hypothalamic-pituitary-adrenal axis which would show some upgrading with increased ACTH (that is claimed to arise from non-pituitary source). ACTH is a peptide that is derived as a sequel of cleavage of a larger precursor POMC pro-opiomelanocortin giving rise to peptides including B-endorphins, ACTH and MSH and its placental source was detected so the placenta is actually taking some of the hypothalamus functions [5-7].

Cortisol level in both forms total and free will increase substantially but still maintaining diurnal rhythm and elevated level could be attributed to elevated level of cortisol binding protein (due to estrogen effect on the liver to increase CBG synthesis) placental synthesis of CRH and ACTH and less sensitivity of the pituitary to negative feedback effect of cortisol [8-10]. Then cortisol level will fall gradually post-partum over days.

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Mineralo-cortocids with Pregnancy

Pregnancy is associated with dramatic vascular changes showing increased cardiac output by about 25-50% with reduced vasuclar resistance and increased intravascular volume by about 45% and on the contrary blood pressure is reduced due to reduced peripheral resistance with increase of extracellular fluid compartment by 4-6 litres all these changes are associtaed with upgrading of the Renin-Angiotensin-Aldosterone system (RAA) where plasma renin activity increases seven folds over non pregnant level [8,11].

Regeneration Potential

After Thomson et al. [12] first described human embryonic stem cells 1998 then at 2006 a great achievement was accomplished by Shinya Yamanaka and his team which is the induction of pluripotent stem cells via introduction of transcription factors (Oct4, Sox2, KLf4 and C-myc) to the genome of well differentiated cells to reset its genetic set up back to stem cell status with pluri potency potential which is known as IPSc (Induced Pluripotent Stem Cells) [13]. Other teams successfully did reprogramming of the already differentiated cells(specialized cells) such as skin fibroblast to resume stemness properties via using other combination of transcription factors so that these cells will have again the capability to differentiate into any cell type (ectoderm, endoderm or mesoderm cell type). So the question was raised about the potential of tissues to regenerate after injury ?

The adrenals were subject for studies to elicit its regeneration potential but still available studies are laboratory based and no available clinical studies yet. The adrenal cortex found to have a continuous renewal driven by hormonal stimulation and a lineage conversion to maintain its function so functional ZG cells differentiate into ZF cell type. This lineage conversion is dependent on the steroidogenic factor-1(Sf-1) and its absence hindered ability of ZG cells to differentiate into ZF cells [14]. Animal studies also showed ZF cells still maintained despite complete deletion of Sf-1 and it was concluded that ZF have other resources to give renewal such as presumed progenitor ZF stem cells known as progenitor cells or stem cells in the sub-capsular area that can bypass the ZG status and give rise to ZF cell type [14]. So basically the adrenal cortex is a very dynamic and plastic organ [14] working in conjunction with and under control of other hormonal loops to maintain life with a reasonable regeneration reserve.

Adrenal Insufficiency (A.I.)

Adrenal insufficiency is a rare disorder with reported incidence in some studies 0.44 per 100,000 population per year [15].

Etiology

Primary: When the adrenals do not secrete adequate amounts of cortisol despite adequate ACTH secretion. The commonest cause recently is autoimmune destruction of the adrenals (autoimmune adrenalitis)including humeral and cell mediated autoimmune process resulting in Addison disease particularly due to T&B lymphocytes against the steroid synthetic system and anti 25-hydroxylase which was found in more than 80% of cases [15-17].

Associations in primary adrenal insufficiency: Association of adrenal insufficiency with HLA class II DR3-DQ2/DRB1*0404-DQ8 genotype was found and its presence predicted early onset [15,18]. Also familial trend found in 10% of cases and first degree relatives have increased risk of adrenal insufficiency. Also association with other autoimmune conditions found in about two thirds of cases with the thyroid disease accounting for the highest association both thyrotoxicosis and hypothyroid [15,18]. In some studies significant association of adrenal insufficiency found with celiac disease and vice versa so they recommended for patients with either condition to check for the other [19,20].

The Biological reserve: It is clear that most if not all vital functions have reasonably good reserve to maintain function and life even if some loss takes place. Due to this usual trend of great reserve once de-compensation takes place this means that the reserve is no longer able to withstand the needs. Same principle applies here where the adrenal insufficiency usually starts to manifest if most of the adrenal cortisol secreting cells are damaged (almost 90% of cells are lost) [21].

It is important at this point to show that the process of autoimmune adrenalitis -which is the commonest cause of A.I - the de-compensation would go through four phases till becomes clinically overt [18]:

- Increased plasma renin activity with normal/low aldosterone (stage 1).

- Low cortisol response after i.v. administration of ACTH (stage 2).

- Increased ACTH (stage 3).

- Low basal cortisol (stage 4).

May be that is why the diagnosis sometimes delayed or even challenging. This autoimmune adrenal insufficiency could be isolated or part of a wider spectrum of poly-endocrine immune insufficiency where there are other co-existing conditions. There are two types of well described poly-endocrine insufficiency:

Type I starts in pediatric age inherited as autosomal recessive disorder involving the AIRE gene on chromosome 21 [22]. This would manifest with hypo-Para-thyroidism, hypogonadism, pernicious anemia and chronic candida infection.

Type II in children and young adults known as Schmidt syndrome shows autosomal inheritance with variable penetrance [23]. This would manifest with hypo-adrenalism, hypothyroid, diabetes mellitus and occasionally vitiligo [21].

Non Immune Causes of Primary Adrenal Insufficiency

T.B which was the commonest cause in the past found in the majority of autopsies of adrenal insufficiency cases but today this is greatly replaced with other causes in particular the autoimmune process.

Malignant cell infiltrate of the adrenals. But it was found that in most cases of adrenal infiltration with malignant cells still residual adrenal tissue is capable of maintaining needs even with stress [21,24]; chronic infections such as Fungal infection e.g. histoplasmosis and paracoccidiomycosis in endemic areas [25]. And others such as syphilis and African trypanosomiasis.

For HIV, adrenal insufficiency usually related to other illnesses such as infections and malignancy. Vascular events: adrenal infarction due to hemorrhage or adrenal vein thrombosis were reported as causes of acute adrenal in-sufficiency particularly in cases with sepsis such as meningococcemia known as Waterhouse-Fridchrisen syndrome but this is reported also with other bacterial infections such as pseudomonas, pneumococci, neiserria gonorrhea, *E. coli* and hemophilus influenza. Also adrenal hemorrhage was reported to be related to cases with acute major illness causing adrenal stress such as burn and cerebrovascular accidents in particular patients taking anticoagulants [26]. In a review report thromboembolism, coagulopathy and postoperative status were

the major risk factors for adrenal hemorrhage and what makes things more difficult is the presentation as it would manifest with abdominal pain, loss of appetite, nausea, vomiting, fever, disturbed conscious level and abdominal rigidity as well as other laboratory findings such as drop of hemoglobin so it would mimic presentation of acute abdomen [27]. Other reports showed thrombocytopenia including Heparin Induced Thrombocytopenia (HIT), heparin exposure more than three days and sepsis are the most significant and independent risk factors for bilateral adrenal hemorrhage [28].

Drugs: Drugs that inhibit steroid synthesis are claimed to play role for adrenal insufficiency but usually the compensatory mechanisms such as increased ACTH or remnant partial enzyme activity makes the adrenal suppression not significant but it could be clinically manifest in case of predisposed patients (those with underlying abnormal adrenal function). These drugs include ketoconazole, fluconazole, metyrapone, suramin [29], phenytoin [30] and rifampicin [31]. Rifampicin in particular was reported to precipitate addisonian crisis in patients with adrenal insufficiency well controlled on cortisol supplement and so it is recommended to at least double the steroid replacement in adrenal insufficiency cases on start of rifampicin [31].

Pseudohypoadrenalism

This entity is known in the literature as functional adrenal insufficiency. During severe illness about 24% of cases has decreased cortisol levels [32]. The underlying mechanism is not fully understood but there are some possibilities:-The effect of cytokines and inflammatory mediators on the hypothalamus-pituitary-adrenal system This hypothesis is supported by animal studies that showed role for IL-6 on the HPA. It was demonstrated that in stressed IL-6 transgenic mice the ACTH secretion was either steady or reduced -which is the case in clinical practice - while adrenal corticosteroids and AVP levels elevated [33]. So there is some sort of depression of the hypothalamus-pituitary system with blunting of the ACTH response after long standing ACTH secretagogue stimulation in addition to possible steroid inhibition feedback effect [33]. IL-1 may also contribute to the modulation of the HPA because there is concurrent IL-1a/b mRNA expression with the transgenic IL-6 expression [33].

Here we need to draw attention that this hypothesis is actually very close to the proposed mechanism for sick thyroid syndrome. In sick euthyroid syndrome cytokines in particular IL-1, IL-6, tumor necrosis factor TNF-alpha and interferon-beta are proposed to act on hypothalamus-pituitary to suppress secretion of TRH and TSH [34].

Another finding in animal studies: adrenal glands in animals subjected to shock status showed areas of necrosis [35]. This finding is related to structural changes of the gland mostly related to interrupted blood supply during shock as part of global hypo-perfusion. This could be involved in the pathogenesis of this transient status of hypo-adrenalism in critically ill patients and the gland through its regenerative potential with lineage conversion and cell renewal process recovers function after resolution of the underlying illness.

This entity was further evaluated in a study focused on cortisol level-both total and free forms-in critically ill patients. The study started from the point that cortisol is highly protein bound almost 90% and mostly to CBG (cortisol binding globulin) [1] and critical illness could be associated with hypo-albuminuria and hypoproteinemia so the matter of hypocortisolism may be related to way of measurement rather than true hypoadrenalism.

The results showed that about 40% of cases of apparently hypoadrenalism during critical illness actually had normal adrenal function and this pseudohypoadrenalism was due to hypoalbuminemia so it is recommended to check free cortisol level rather than the total cortisol before start steroid replacement [36]. So pathogenesis of this entity could be multifactorial involving cytokines and inflammatory mediators effect on the hypothalamus-pituitary-adrenal axis, transient interruption of blood supply to the adrenal glands and effect of hypoproteinemia on the bound cortisol levels.

Also possibility of hypoadrenalism as part of hypopituitarism is there through down grading of the entire HPA axis and this possibility is supported by the finding of low thyroxin, cortisol and gonadotropins in some critical illness cases which recovered to normal after stabilization of the acute status [37] but further studies are required to find out clear correlation of this entity of hypoadrenalsim in critical illness with sick euthyroid syndrome and deficiency of other pituitary hormones.

Management

Low cortisol level in a percent of critically ill patients in addition to the known cortisol role as a potent anti-inflammatory raised the concern of use of steroids in such patients and if any morbidity or mortality benefit?

The pharmacologic doses of steroids (defined as hydrocortisone exceeding 300 mg/d) did not improve prognosis in severe sepsis, actually increased mortality related to secondary infection was found in the subgroup of patients with acute renal failure (creatinine exceeding 2 mg/dl) [38].

But some promising results in a small study showed significant improvement with less vasopressor requirements in critically ill patients after physiologic doses of steroids(hydrocortisone 100-300 mg/d) [39].

The interesting point in this study is that cosyntropin test showed cortisol levels higher than classic hypo-adrenal states so the authors concluded a functional hypoadrenalsim in these multisystem critically ill patients rather than true hypoadrenalism state [39]. So no benefit from pharmacologic cortisol doses but physiologic doses of cortisol could be beneficial [32].

So the term pseudohypoadrenalism is more appropriate because it is not true hypoadrenalism but actually it is a transient phenomenon related to extra adrenal events in addition to the method of cortisol level estimation that would be misleading due to hypoproteinemia.

From the previous facts routine screening for adrenal insufficiency during critical illness is not recommended but clinicians should consider steroid replacement with physiologic doses in certain situations such as: persistent hypotension, fever for no good reason or difficult weaning from ventilator. Still further studies are required to standardize this approach and collect morbidity and mortality data [32,35].

Secondary/tertiary adrenal insufficiency

This may take place due to several reasons such as trauma, surgical excision of parts of hypothalamus or pituitary, tumors such as pituitary adenomas - the most common craniopharyngioma-or metastases, infiltrate with sarcoidosis, Langerhans cell hisiocytosis, radiation, abrupt withdrawal of steroids after long term use including forms of cortisol other than oral or injection such as inhalers and creams (particularly if large area and frequent use), severe interruption of blood supply of the pituitary such as in Sheehan syndrome [40-42]. Cases of traumatic brain injury and subarachnoid hemorrhage also may show evidence of hypopituitarism [43].

Hemochromatosis both hereditary and secondary can cause

primary or secondary adrenal failure due to iron deposition in adrenals or pituitary respectively [40].

Some reports about isolated ACTH deficiency including autoimmune hypo-physistis which is a rare entity and challenging to diagnose [44-46]. It is important to note that in secondary and tertiary hypoadrenalsim mineralocorticoid secretion is still active as the zona glomerulosa is still responsive to renin-angiotensin system [8].

Presentation

The adrenal insufficiency usually presents with non-specific symptoms of fatigue, generalized weakness, loss of appetite and weight loss that is progressing gradually. Skin pigmentation due to increased synthesis of pro-opiomelanocortin which is a prohormone that is cleaved to smaller peptides such as ACTH and MSH (Melanocyte Stimulating Hormone) which acts on Melanocortin Receptor 1 (MC-1R) [47,48], leading to skin pigmentation that affects exposed and non-exposed areas and more pronounced in scars and skin creases but this pigmentation will be absent in secondary and tertiary hypoadrenalism due to ACTH deficiency and also exceptionally absent in some cases of primary hypoadrenalism. The pigmentation severity may vary from light tanning to marked generalized pigmentation particularly extensor surfaces, creases and mucosa at the dental-gingival margin [49] and this variability in pigmentation severity could be attributed to the duration of exposure and/or level of ACTH elevation.

Electrolyte disturbance in the form hyponatremia and hyperkalemia that is mainly due to mineralocorticoid deficiency. Sometimes show dramatic changes with marked hyponatremia and significantly elevated potassium but some cases show just subtle alteration from normal. Also this electrolyte disturbance may be absent in secondary and tertiary A.I due to still intact renin-angiotensin-aldosterone system.

Hypotension may be a cardinal finding on first encounter with A.I particularly in addisonian crisis cases. But this is not an absolute finding actually it could be just postural hypotension and occasionally hypotension may not be evident till shock takes place. Hypotension is attributed to volume depletion secondary to anorexia and also effect of steroid depletion on epinephrine synthesis and the negative effect on vascular tone and adaptation to stress [50] and effect of mineralocorticoid deficiency on salt and water renal loss. At this point we want to draw attention to known cases with hypertension that become well controlled off medications with no good reason for that e.g. no significant lifestyle modification that could justify for controlling blood pressure without medications. This aborted hypertension should raise the possibility of adrenal insufficiency.

Increased sensitivity to insulin in diabetics and hypoglycemia in non-diabetics could be encountered as part of the A.I manifestations due to loss of glucocorticoid effect on gluconeogenesis. Cases of thyroid replacement therapy as a sort of metabolic stress-shifting from hypometabolic to eumetabolic status - with treatment of hypothyroidism may uncover adrenal insufficiency to become clinically overt. Of the presentations reported in the literature: abdominal pain, chest pain, fever, abdominal tenderness that could be related to underlying serositis that was reported in autoimmune endocrinopathies. So it is recommended to consider A.I in any case with unexplained abdominal pain [51,52]. Fever particularly in post-operative situations A.I is part of the differential diagnosis but in such case underlying infection should be carefully investigated. Adrenal androgen insufficiency in particular females below age of 40 years would report dry skin, loss of libido, loss of pubic and axillary hair. This is due to adrenal DHEA(S) (Dehydroepiandrosterone Sulfate) deficiency [41,53].

After major trauma there is reported association of adrenal insufficiency after major trauma requiring ICU admission and mechanical ventilation but injury is not an independent predictor of adrenal insufficiency. So it is recommended to consider adrenal insufficiency after major injury [54] but this entity could be due to the pseudohypoadrenalism that we discussed earlier. In the literature also reported cases of auricular cartilage calcification in adrenal insufficiency. This could be related to transient hypercalcemia but the pathogenesis is not clear [55].

Psychiatric Manifestations

Of the presentations that should be considered in adrenal insufficiency because of its remarkable impact on the patient. As in other endocrinopathies psychiatric disorders are part of the spectrum of presentations. In Adrenal insufficiency psychiatric disorders are uncommon but well reported. Actually it could be the first presenting and even the only manifestation. The spectrum of psychiatric disorders associated with A.I is wide including mood and behavioral changes such as depressed mood, apathy, cognitive impairment and poor academic performance, sleep disorders, irritability up to psychotic manifestations, and rarely catatonia and self-mutilation [56-58]. In such psychiatric presentation it is really challenging to diagnose but usually there are some clues that suggest or guide the clinician to consider evaluating for A.I like low BP, pigmentation or electrolyte disturbance but sometimes resistance to psychiatric drugs is the only clue to re-consider the diagnosis. The underlying pathogenesis for such neuropsychiatric manifestations in AI is not clearly identified ,but it could be due to :

The underlying cause that may affect the brain as well as other organs such as T.B., fungal infection, metastatic malignancy, HIV, syphilis or adrenoleucodystrophy. Adrenoleucodystrophy is an X-linked disorder due to VLCFA (very long chain fatty acid accumulation) mainly affects adrenals, brain and gonads and presents during childhood [57,59].

The electrolyte and fluid status disturbance such as hyponatremia and hypovolemia; contribute to the neuropsychiatric manifestations of the adrenal insufficiency. In animal studies adrenalectomy without replacement therapy resulted in selective granule cell loss in the hippocampus and adequate supplement with corticosteroids salvaged the granule cells so the investigators concluded the importance of corticosteroids to maintain integrity of dentate gyrus granule cells in normal brain [57,58,60,61]. Also animal studies showed that glucocorticoid deficiency has negative effect on the prefrontal cortex with impairment of the working memory through reduction of dopamine release and up regulation of D1 receptors [62]. Another postulated mechanism for A.I neuropsychiatric disorders is the increased endorphins secondary to increased synthesis of POMC (pro-opiomelanocortin) as a precursor of other smaller peptides including endorphins. As and endorphins were shown to be elevated in CSF of some schizophrenia cases but still this theory is candidate for further studies [57].

Emergency Presentation

Some cases may present for the first instance with a life threatening acute hypoadrenalism known as addisonian crisis usually precipitated by stress such as infection and this would manifest with shock state including hypotension dizziness and may be fainting and this crisis could be life threatening if not treated promptly. One of the catastrophic presentations of adrenal insufficiency is as part of pituitary apoplexy syndrome when acute pituitary infarction takes place. Presents with acute severe headache, visual impairment and meningism and it is

mostly secondary to hemorrhagic infarction of a pituitary tumor [63].

During pregnancy:

Pregnancy is a normal presentation of abnormal physiology. Our concern here is the HPA axis and RAA system which are physiologically upgraded with elevated levels of ACTH, cortisol and aldosterone. The adrenal insufficiency despite importance of the diagnosis there is potential to be delayed due to overlapping presentations between the physiologic symptoms such as nausea, vomiting and abdominal pains and pathologic manifestations of A.I but if persistent symptoms and electrolyte disturbance clinicians should consider to work up the diagnosis of A.I. Postpartum period in particular is a risky period for uncovering the A.I and this could be attributed to loss of placental/fetal cortisol production [8]. Causes of A.I in pregnancy are same causes as in non-pregnant. Overall the A.I has a wide variety of presentations so it is clear why the diagnosis sometimes substantially delayed and it is recommended for the clinicians to keep low threshold for considering and investigating for such important diagnosis once raised as a possibility according to the clinical scenario.

Diagnosis

The clinical presentation will guide to just suspect the diagnosis. Electrolytes may act as pointers to the diagnosis (low sodium, elevated potassium) but the gold standard to make diagnosis as in other endocrine disorders is the dynamic tests.

ACTH stimulation

Due to the circadian rhythm of cortisol secretion normally the morning cortisol level is higher than the late afternoon and evening levels [64] also it is expected in stress situations to get cortisol level elevated. If suspecting A.I: In terms of absolute figures basal morning cortisol level less than (3 mcg/l or 80 nmol/l) is very suggestive of the diagnosis and more than (19 mcg/l or 524 nmol/l) can rule out the diagnosis [65] but many patients will come to the grey zone in between these two extremes so further evaluation is warranted. While during acute illness with suspected A.I cortisol level less than 250 nmol/l with elevated ACTH level is considered diagnostic of primary A.I [66]. So it is recommended to check both cortisol and ACTH levels but if non-conclusive proceed with synacthen test [66].

Short synacthen test

Short synacthen test as a provocation test to figure out the adrenal response to ACTH stimulation. It is reasonably sensitive and reliable if appropriately utilized and it has the advantage of safety and simplicity as it is done on outpatient basis but with some limitations that would be discussed later. ACTH 250 mcg injected IV or IM then cortisol level is estimated before injection (zero time) then 30-60 minutes after.

Before interpretation of the results an important question actually is to define the normal level of cortisol. This point proved to be not straight forward as studies showed great variability between normal subjects and the distribution was non Gaussian. Also significant differences in the normal response to cosyntropin stimulation were encountered including differences between the two genders (where females show higher response levels after cosyntropin injection) [67]. Even significant differences were found just due to different cortisol assay methods [67]. So interpretation of the test results should take these points into consideration and interpretation of results should refer to the local laboratory references.

Some studies reported comparable results between the small dose cosyntropin 1 mcg and that of 250 mcg [54] but this small dose is not widely available.

Limitation of this test: If the test done early (within four weeks) in the course of secondary and/or tertiary A.I the adrenal glands may still give adequate response with normal cortisol level post cosyntropin injection and this is due to residual cortisol secretagogues as it takes time to get sufficient adrenal atrophy after lack of ACTH stimulation [41].

Insulin tolerance test

This test is considered the most reliable test for assessment of the hypothalamo-hypophysial-adrenal axis [9]. It should be considered in case of suspected secondary adrenal insufficiency, failed synacthen test, patients already on steroid therapy or in case of acute pituitary injury(within two weeks) [68-70].

Limitations: The test is contraindicated in ischemic heart disease and history of seizures. Also should be done in a well observed environment because of potential risk of seizures or fainting due to hypoglycemia. In case of seizures with hypoglycemia-surely the test should be interrupted immediately with immediate resuscitation with IV dextrose-but blood samples at that time -if could be collected-would be very informative as the stress was very significant.

Metyrapone test

Metyrapone blocks the final step in cortisol synthesis [71]. Some reports suggest metyrapone test as a valuable test to evaluate the entire hypothalamo-pituitary-adrenal axis in particular secondary adrenal insufficiency cases [71] as an alternative to insulin tolerance test but this test is not widely available.

Corticotrophin Releasing Hormone (CRH) test

The CRH is a hypothalamic hormone regulates the pituitary ACTH secretion. This test was advocated to differentiate secondary from tertiary adrenal insufficiency but it is also not widely available [72].

An important item that should not be overlooked during the process of diagnosis of A.I is to look for the underlying cause. The underlying cause could raise possibility of other comorbidities that should be addressed on its own for instance in autoimmune adrenalitis it may be associated with other autoimmune diseases or if A.I caused by infection it should receive the appropriate antimicrobial therapy. Also the diagnosis would be of value for other family members because of the familial trend of the autoimmune A.I.

At this point of work up it may be helpful to find a clue from the imaging studies that may guide the diagnosis. One study looked at different CT findings in A.I and if any correlation between CT imaging findings of the adrenals and the underlying diagnosis. More than 80% of the adrenals were enlarged in case of insufficiency due to infiltration with malignant cells or T.B (within the first two years of infection) and about 50% of T.B. cases showed adrenal calcification. While all cases of idiopathic Addison disease showed small or even undetectable adrenals and no calcification [73,74].

Pitfalls in the diagnosis

These are points we want to draw attention of clinicians to them:

- Keep in mind the entity of pseudohypoadrenalism (functional adrenal insufficiency)in which the cortisol level is less than expected which is encountered in critically ill patients and in good percent of cases. It is due to decreased cortisol binding globulin level with normal free cortisol and in some patients due to some sort of downgrading of

all vital organs including the pituitary-adrenal axis and usually recovers after stabilization of the patient with no benefit from treatment with pharmacologic cortisol.

- Pigmentation as a cardinal sign of adrenal insufficiency is absent in secondary and tertiary A.I and some primary adrenal insufficiency cases.

- In secondary adrenal insufficiency response to ACTH test could be adequate if the test done early -defined as within four weeks-in the course of illness so that in such case no enough time for significant adrenal atrophy to take place [41].

- The first presentation could be misleading as in case of neuropsychiatric disorders so clinicians and psychiatrists should be aware that A.I could present with mood and/or behavioral changes.

- First presentation with shock and fever that would be diagnosed as septic shock. Definitely we have to address the infectious possibility but if in doubt we have also to address the possibility of A.I till investigate properly later on.

- In post-operative cases A.I may present with abdominal pain with acute drop of hemoglobin and fever so it is part of the differential diagnosis of acute abdomen particularly if ruled out other causes.

Treatment

The treatment is based on glucocorticoid with or without mineralocorticoid replacement. The recommended dose usually 15-25 mg hydrocortisone/day in 2-3 divided doses which is equivalent to the physiologic daily synthesis of cortisol 15.7 μmol/day·m^2; 5.7 mg/m^2·day [1,41,75]. First dose with waking up and last dose not less than 6 hours before bed time [66]. In one study weight adjusted hydrocortisone thrice daily dosing was recommended to be taken before meals to enhance absorption and avoid overdosing [76].

In case of co-prescription of other medications we should exercise caution and consider increasing the cortisol dose if co-prescriped enzyme inducer. Caution also should be taken to avoid supra-physiologic doses that may be unnecessary and even would induce iatrogenic Cushing syndrome. In one study the IOP (intraocular pressure) was shown to be significantly higher with the 20 mg AM dose as compared with the 10 mg AM dose [77] and this is an example to show that overdosing should be avoided because of potential side effects. The new forms of dual release preparations could represent a better option for A.I patients to mimic the physiologic pattern of cortisol release with less side effect profile [78] but this form is not widely available.

After start glucocorticoid replacement consider mineralocorticoid replacement as well. There are reports about addisonian crises despite regular glucocorticoid supplement due basically to mineralocorticoid deficiency [79,80]. So it is recommended for most patients with primary A.I 50-200 µg fludrocortisone OD dose [66]. But if hypertension develops reduce the fludrocortisone dose but do not stop [66] as it is still required for adjustment of fluid and electrolyte status.

After start treatment monitoring adequacy of glucocorticoid replacement to make sure of adequate replacement and avoid overdosing is really important task but no clear consensus about the optimal way to monitor the adequacy of replacement. The follow up would depend on clinical and biochemical parameters: relief of symptoms is a priority so it is advisable to keep on the lowest effective dose to relieve symptoms mainly postural hypotension and achieve better appetite and wellbeing and on the other hand avoid unnecessary over-replacement. Also corrected electrolyte imbalance and normalized plasma rennin activity. But clinicians should not attempt to normalize plasma renin activity if the other parameters are well maintained such as normal electrolytes and blood pressure [81].

ACTH check was suggested as a follow up parameter but it did not prove adequate way to assess the proper dosing because in primary A.I it was shown that the pituitary ACTH secretion shows significant variability in response to cortisol supplement and this could be related to prolonged interruption of the feedback loop between adrenal and the hypothalamus-pituitary system [82]. So we cannot adjust cortisol doses based on ACTH level. Also ACTH monitoring is totally invalid as a follow up test in secondary and tertiary AI. The serum cortisol day curves were also proposed as a monitoring method but it did not prove to be a reliable way to monitor the replacement therapy. Also BMD (bone mineral density) assessment was shown normal in all subjects so it is not indicated to monitor BMD in A.I patients on treatment unless other indication for that according to the clinical situation [83].

Monitoring of A.I patients should be done at least annually with evaluation of general status, wellbeing, apetite, weight, activity, blood pressure and electrolytes. In pan hypopituitarism cortisol replacement should start prior to thyroid hormone replacement as thyroid hormone supplement without adequate glucocorticoid supplement may precipitate adrenal decompensation and even crisis.

In case of stress such as infections, trauma, surgery there is physiologic response to stress by upgrading the action of the hypothalamo-pituitary-adrenal axis to increase hormones of stress including ACTH and cortisol [84] so it is recommended to increase the replacement dose by double or even triple to mimic the physiologic changes and meet the stress requirements.

Patients planned for surgery

High dose cortisol replacement was the trend but actually this concept has been challenged in one report that reviewed the available data and recommended against high dose cortisol replacement. They recommended to adjust the dose according to the baseline preoperative dose and the nature of surgery and anesthesia (is it minor procedure under local anesthesia versus major surgery) [85]. Actually the perioperative steroid dose management is discussed elsewhere and beyond the scope of this article we just recommend expert handling in case of established adrenal insufficiency undergoing surgery.

DHEA replacement : is not well standardized approach and not routinely recommended [66]. Some endocrinologists suggested it for women with A.I to counteract the hypo androgenic state if still well-being is a concern despite adequate glucocorticoid and mineralocorticoid replacement. But apart from this target studies done to figure out if such DHEA supplement may have positive protective effect on endothelial function or lipid profile but results did not show any favorable effect [86] even some reports denoted unfavorable effects on the lipid profile as it decreased the HDL level [87].

During pregnancy

Diagnosis and treatment of A.I during pregnancy is of paramount importance for mother and fetus, albeit it is not routine to screen for A.I but it depends on clinical presentation. Pregnant with history of adrenal surgery should be monitored carefully and replacement treatment should not depend on symptoms even asymptomatic cases may be offered treatment as the outcome may be catastrophic [88]. Doses of hydrocortisone will remain same till third trimester to be increased by 2.5-10 mg/d going with normal physiologic changes of increased

free cortisol third trimester [89] also fludrocortisones dose should be increased in late pregnancy and monitoring would be based on clinical assessment including salt craving, blood pressure monitoring and electrolytes but not plasma renin activity as it is physiologically elevated in late pregnancy [89]. During labor 100 mg I.V hydro-cortisone should be given and repeat every 6 hours if necessary also oral dose should be doubled for 1-2 days post-partum [89].

Adrenal crisis

A life threatening condition with shock state that should be treated immediately. Waiting for confirmatory tests is inappropriate and clinicians should consider immediate volume expansion with I.V saline and I.V steroid preferably dexamethasone. It is better avoid hydrocortisone and cortisone -if possible- to give room for later evaluation of adrenal function as dexamethasone will not interfere with cortisol assays but still it would suppress ACTH release. If hydrocortisone is the available form; 100 mg hydrocortisone I.V immediately followed by 100 mg IV Q 6-8 hrs. till stabilization of hemodynamic status [89]. In acute situations I.M cortisone acetate should be avoided [90] as it is inactive form. Again clinicians should not overlook treatment of the underlying cause.

Self-recovery

Some cases of adrenal dysfunction due to T.B were reported to recover adrenal function after successful treatment of T.B. [91] but other reports on the other hand challenged this concept and denoted that adrenal function did not show any recovery within 2-5 years of follow up [92-96]. There is report also about adrenal function recovery after prolonged treatment of fungal infection [25]. Cases post traumatic brain injury and subarachnoid hemorrhage showing evidence of hypopituitarism some of them do recover with time [43]. It seems that to recover function or not depends on the degree of damage affected the adrenals which also depends on how early is the diagnosis and how effective is the treatment.

Also the issue of recovery may be related to the self-regenerative potential of the adrenals including the lineage conversion process that may allow some regeneration and functional cell type switch from zona glomerulosa to zona fasiculata cell type under influence of hormonal stimulation [14]. This also would depend on residual functional cells in the adrenals rather than cases with marked cell loss.

Patient and family awareness

Part of the management of these patients is actually to have a medical card and wear a medical alert like bracelet indicating the diagnosis, the medication type and dosage and the medical service contact numbers in case of emergency [97,98]. An important aspect of treatment also is the patient and family education about the diagnosis, how to handle the dose in case of stress such as infection and how to inject with rescue dose of cortisol in case of emergency.

Summary and Recommendations

Adrenal glands play critical role for human survival, act under higher meticulous control from the hypothalamus-pituitary system and renin angiotensin system. Adrenal insufficiency could be primary (related to adrenal related cause) or secondary or tertiary (pituitary or hypothalamus related causes). Adrenal insufficiency may present with very non-specific manifestations but main features: pigmentation, hypotension that may start with postural hypotension and electrolyte disturbance with exceptions for all these cardinal findings.

Adrenal insufficiency should be considered as part of differential diagnosis for any unexplained loss of appetite and weight loss after rule out other more likely causes according to the clinical scenario.

Also clinicians should not depend on pointers to confirm or rule out this diagnosis. Mean by pointers the laboratory tests that are expected to show some classic changes with adrenal insufficiency such as low sodium and elevated potassium because these changes may be subtle or even absent. Short synacthen test is reasonably reliable and easily applicable test with some limitations that should be kept in mind particularly if negative results with still high clinical suspection of the diagnosis. Clinicians should not hesitate to replace with stress dose of steroid in acute situations, because of the life threatening nature of adrenal crisis if not promptly treated, then consider formal evaluation later on. At the end want to stress on the importance of patient and family awareness of the diagnosis and emergency measures.

References

1. Eileen K Corrigan (2007) Adrenal Insufficiency (Secondary Addison's or Addison's Disease). NIH Publication 90-3054.
2. Autoimmune polyendocrine syndrome, Type I, with or without reversible metaphyseal dysplasia; APS1. OMIM #240300.
3. Autoimmune polyendocrine syndrome, Type II; APS2. OMIM #269200.
4. Phyllis W Speiser (2015) Pediatric Adrenal Insufficiency (Addison Disease).
5. Guyton and Hall (1956) Text of medical Physiology, (9thedn) Chp. 75-77.
6. Martha H. Kidane (2015) Harrison principles of internalmedicine. (18thedn) Chp. 339 & 342.
7. Erichsen MM, Løvås K, Skinningsrud B, Wolff AB, Undlien DE, et al. (2009) Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency: observations from a Norwegian registry. J Clin Endocrinol Metab 94: 4882-4890.
8. Kasperlik-Zaluska AA, Migdalska B, Czarnocka B, Drac-Kaniewska J, Niegowska E, et al. (1991) Association of Addison's disease with autoimmune disorders--a long-term observation of 180 patients. Postgrad Med J 67: 984-987.
9. Husebye ES, Løvås K (2009) Immunology of Addison's disease and premature ovarian failure. Endocrinol Metab Clin North Am 38: 389-40, ix.
10. Betterle C, Scalici C, Presotto F, Pedini B, Moro L, et al. (1988) The natural history of adrenal function in autoimmune patients with adrenal autoantibodies. J Endocrinol 117: 467-475.
11. Elfström P, Montgomery SM, Kämpe O, Ekbom A, Ludvigsson JF (2007) Risk of primary adrenal insufficiency in patients with celiac disease. J Clin Endocrinol Metab 92: 3595-3598.
12. Myhre AG, Aarsetøy H, Undlien DE, Hovdenak N, Aksnes L, et al. (2003) High frequency of coeliac disease among patients with autoimmune adrenocortical failure. Scand J Gastroenterol 38: 511-515.
13. Vita JA, Silverberg SJ, Goland RS, Austin JH, Knowlton AI (1985) Clinical clues to the cause of Addison's disease. Am J Med 78: 461-466.
14. Sun ZH, Nomura K, Toraya S, Ujihara M, Horiba N, et al. (1992) Clinical significance of adrenal computed tomography in Addison's disease. Endocrinol Jpn 39: 563-569.
15. Penrice J, Nussey SS (1992) Recovery of adrenocortical function following treatment of tuberculous Addison's disease. Postgrad Med J 68: 204-205.
16. Bhatia E, Jain SK, Gupta RK, Pandey R (1998) Tuberculous Addison's disease: lack of normalization of adrenocortical function after anti-tuberculous chemotherapy. Clin Endocrinol (Oxf) 48: 355-359.
17. Washburn RG, Bennett JE (1989) Reversal of adrenal glucocorticoid dysfunction in a patient with disseminated histoplasmosis. Ann Intern Med 110: 86-87.
18. Xarli VP, Steele AA, Davis PJ, Buescher ES, Rios CN, et al. (1978) Adrenal hemorrhage in the adult. Medicine (Baltimore) 57: 211-221.
19. Rao RH, Vagnucci AH, Amico JA (1989) Bilateral massive adrenal hemorrhage: early recognition and treatment. Ann Intern Med 110: 227-235.

20. Kovacs KA, Lam YM, Pater JL (2001) Bilateral massive adrenal hemorrhage. Assessment of putative risk factors by the case-control method. Medicine (Baltimore) 80: 45-53.

21. Cedermark BJ, Sjöberg HE (1981) The clinical significance of metastases to the adrenal glands. Surg Gynecol Obstet 152: 607-610.

22. Ashby H, DiMattina M, Linehan WM, Robertson CN, Queenan JT, et al. (1989) The inhibition of human adrenal steroidogenic enzyme activities by suramin. J Clin Endocrinol Metab 68: 505-508.

23. Keilholz U, Guthrie GP Jr (1986) Adverse effect of phenytoin on mineralocorticoid replacement with fludrocortisone in adrenal insufficiency. Am J Med Sci 291: 280-283.

24. Kyriazopoulou V, Parparousi O, Vagenakis AG (1984) Rifampicin-induced adrenal crisis in addisonian patients receiving corticosteroid replacement therapy. J Clin Endocrinol Metab 59: 1204-1206.

25. Mackenzie JS, Burrows L, Burchard KW (1998) Transient hypoadrenalism during surgical critical illness. Arch Surg 133: 199-204.

26. Hamrahian AH, Oseni TS, Arafah BM (2004) Measurements of serum free cortisol in critically ill patients. N Engl J Med 350: 1629-1638.

27. Burke CW (1985) Adrenocortical insufficiency. Clin Endocrinol Metab 14: 947-976.

28. De Luis DA, Aller R, Romero E (1998) Isolated ACTH deficiency. Horm Res 49: 247-249.

29. Jacobs TP, Whitlock RT, Edsall J, Holub DA (1988) Addisonian crisis while taking high-dose glucocorticoids. An unusual presentation of primary adrenal failure in two patients with underlying inflammatory diseases. JAMA 260: 2082-2084.

30. Cronin CC, Callaghan N, Kearney PJ, Murnaghan DJ, Shanahan F (1997) Addison disease in patients treated with glucocorticoid therapy. Arch Intern Med 157: 456-458.

31. Tucker WS Jr, Niblack GD, McLean RH, Alspaugh MA, Wyatt RJ, et al. (1987) Serositis with autoimmune endocrinopathy: clinical and immunogenetic features. Medicine (Baltimore) 66: 138-147.

32. Castaldo ET, Guillamondegui OD, Greco JA 3rd, Feurer ID, Miller RS, et al. (2008) Are adrenal injuries predictive of adrenal insufficiency in patients sustaining blunt trauma? Am Surg 74: 262-266.

33. Randeva HS, Schoebel J, Byrne J, Esiri M, Adams CB, et al. (1999) Classical pituitary apoplexy: clinical features, management and outcome. Clin Endocrinol (Oxf) 51: 181-188.

34. Tobin MV, Aldridge SA, Morris AI, Belchetz PE, Gilmore IT (1989) Gastrointestinal manifestations of Addison's disease. Am J Gastroenterol 84: 1302-1305.

35. Zuckerman-Levin N, Tiosano D, Eisenhofer G, Bornstein S, Hochberg Z (2001) The importance of adrenocortical glucocorticoids for adrenomedullary and physiological response to stress: a study in isolated glucocorticoid deficiency. J Clin Endocrinol Metab 86: 5920-5924.

36. Barnett AH, Espiner EA, Donald RA (1982) Patients presenting with Addison's disease need not be pigmented. Postgrad Med J 58: 690-692.

37. Tsatmali M, Ancans J, Yukitake J, Thody AJ (2000) Skin POMC peptides: their actions at the human MC-1 receptor and roles in the tanning response. Pigment Cell Res 13 Suppl 8: 125-129.

38. Rousseau K, Kauser S, Pritchard LE, Warhurst A, Oliver RL, et al. (2007) Proopiomelanocortin (POMC), the ACTH/melanocortin precursor, is secreted by human epidermal keratinocytes and melanocytes and stimulates melanogenesis. FASEB J 21: 1844-1856.

39. Calvo Catalá J, Hortelano Martínez E, González-Cruz Cervellera MI, Climent Díaz B, Ortega Gonzâlez E, et al. (1994) [Calcification of auricular cartilages in a patient with adrenal insufficiency: presentation of a case and review of the literature]. An Med Interna 11: 496-498.

40. Agut Fuster MA, Agulles Fornés MJ, Ferrer Rodríguez A, Ramos Martínez MJ, del Campo Biosca J, et al. (2007) [Calcification of auricular cartilages in adrenal insufficiency]. Acta Otorrinolaringol Esp 58: 167-168.

41. Farah Jde L, Lauand CV, Chequi L, Fortunato E, Pasqualino F, et al. (2015) Severe psychotic disorder as the main manifestation of adrenal insufficiency. Case Rep Psychiatry 2015: 512430.

42. Anglin RE, Rosebush PI, Mazurek MF (2006) The neuropsychiatric profile of Addison's disease: revisiting a forgotten phenomenon. J Neuropsychiatry Clin Neurosci 18: 450-459.

43. Sloviter RS, Valiquette G, Abrams GM, Ronk EC, Sollas AL, et al. (1989) Selective loss of hippocampal granule cells in the mature rat brain after adrenalectomy. Science 243: 535-538.

44. Gould E, Woolley CS, McEwen BS (1990) Short-term glucocorticoid manipulations affect neuronal morphology and survival in the adult dentate gyrus. Neuroscience 37: 367-375.

45. Mizoguchi K, Ishige A, Takeda S, Aburada M, Tabira T (2004) Endogenous glucocorticoids are essential for maintaining prefrontal cortical cognitive function. J Neurosci 24: 5492-5499.

46. Narayan V, Narayanaswamy JC, Krishnakanth M, Muralidharan K (2008) Atypical Neuropsychiatric Presentation of Addison's Disease: A Case Report. Prim Care Companion J Clin Psychiatry 10: 412-413.

47. #300100; ICD10CM: E71., E71.529; ORPHA: 13939, 139399, " qtip_title="ICD+ for #300100" data-hasqtip="101"ICD+, ADRENOLEUKODYSTROPHY; ALD

48. Abdel-Motleb M1 (2012) The neuropsychiatric aspect of Addison's disease: a case report. Innov Clin Neurosci 9: 34-36.

49. Nieman LK (2003) Dynamic evaluation of adrenal hypofunction. J Endocrinol Invest 26: 74-82.

50. Arlt W (2009) The approach to the adult with newly diagnosed adrenal insufficiency. J Clin Endocrinol Metab 94: 1059-1067.

51. Stewart PM, Corrie J, Seckl JR, Edwards CR, Padfield PL (1988) A rational approach for assessing the hypothalamo-pituitary-adrenal axis. Lancet 1: 1208-1210.

52. Clark PM, Neylon I, Raggatt PR, Sheppard MC, Stewart PM (1998) Defining the normal cortisol response to the short Synacthen test: implications for the investigation of hypothalamic-pituitary disorders. Clin Endocrinol (Oxf) 49: 287-292.

53. Boner AL (2001) Effects of intranasal corticosteroids on the hypothalamic-pituitary-adrenal axis in children. J Allergy Clin Immunol 108: S32-39.

54. Gonzálbez J, Villabona C, Ramón J, Navarro MA, Giménez O, et al. (2000) Establishment of reference values for standard dose short synacthen test (250 microgram), low dose short synacthen test (1 microgram) and insulin tolerance test for assessment of the hypothalamo-pituitary-adrenal axis in normal subjects. Clin Endocrinol (Oxf) 53: 199-204.

55. Arlt W, Justl HG, Callies F, Reincke M, Hübler D, et al. (1998) Oral dehydroepiandrosterone for adrenal androgen replacement: pharmacokinetics and peripheral conversion to androgens and estrogens in young healthy females after dexamethasone suppression. J Clin Endocrinol Metab 83: 1928-1934.

56. Agha A, Rogers B, Sherlock M, O'Kelly P, Tormey W, et al. (2004) Anterior pituitary dysfunction in survivors of traumatic brain injury. J Clin Endocrinol Metab 89: 4929-4936.

57. Giordano G, Aimaretti G, Ghigo E (2005) Variations of pituitary function over time after brain injuries: the lesson from a prospective study. Pituitary 8: 227-231.

58. Caturegli P, Lupi I, Landek-Salgado M, Kimura H, Rose NR (2008) Pituitary autoimmunity: 30 years later. Autoimmun Rev 7: 631-637.

59. Esteban NV, Loughlin T, Yergey AL, Zawadzki JK, Booth JD, et al. (1991) Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. J Clin Endocrinol Metab 72: 39-45.

60. Fiad TM, Kirby JM, Cunningham SK, McKenna TJ (1994) The overnight single-dose metyrapone test is a simple and reliable index of the hypothalamic-pituitary-adrenal axis. Clin Endocrinol (Oxf) 40: 603-609.

61. Schulte HM, Chrousos GP, Avgerinos P, Oldfield EH, Gold PW, et al. (1984) The corticotropin-releasing hormone stimulation test: a possible aid in the evaluation of patients with adrenal insufficiency. J Clin Endocrinol Metab 58: 1064-1067.

62. Nieman LK, Loriaux DL (1989) Corticotropin-releasing hormone: clinical applications. Annu Rev Med 40: 331-339.

63. Fariss BL, Hane S, Shinsako J, Forsham PH (1978) Comparison of absorption of cortisone acetate and hydrocortisone hemisuccinate. J Clin Endocrinol Metab 47: 1137-1140.

64. Purnell JQ, Brandon DD, Isabelle LM, Loriaux DL, Samuels MH (2004) Association of 24-hour cortisol production rates, cortisol-binding globulin, and plasma-free cortisol levels with body composition, leptin levels, and aging in adult men and women. J Clin Endocrinol Metab 89: 281-287.

65. Crown A, Lightman S (2005) Why is the management of glucocorticoid deficiency still controversial: a review of the literature. Clin Endocrinol (Oxf) 63: 483-492.

66. Li Voon Chong JS, Sen J, Johnson Z, Kyle G, MacFarlane IA (2001) Hydrocortisone replacement dosage influences intraocular pressure in patients with primary and secondary hypocortisolism. Clin Endocrinol (Oxf) 54: 267-271.

67. Johannsson G, Nilsson AG, Bergthorsdottir R, Burman P, Dahlqvist P, et al. (2012) Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation. J Clin Endocrinol Metab 97: 473-481.

68. Tuchelt H, Dekker K, Bähr V, Oelkers W (2000) Dose-response relationship between plasma ACTH and serum cortisol in the insulin-hypoglycaemia test in 25 healthy subjects and 109 patients with pituitary disease. Clin Endocrinol (Oxf) 53: 301-307.

69. Feek CM, Ratcliffe JG, Seth J, Gray CE, Toft AD, et al. (1981) Patterns of plasma cortisol and ACTH concentrations in patients with Addison's disease treated with conventional corticosteroid replacement. Clin Endocrinol (Oxf) 14: 451-458.

70. Arlt W, Rosenthal C, Hahner S, Allolio B (2006) Quality of glucocorticoid replacement in adrenal insufficiency: clinical assessment vs. timed serum cortisol measurements. Clin Endocrinol (Oxf) 64: 384-389.

71. Mah PM, Jenkins RC, Rostami-Hodjegan A, Newell-Price J, Doane A, et al. (2004) Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency. Clin Endocrinol (Oxf) 61: 367-375.

72. Nakamura A, Osonoi T, Terauchi Y (2010) Relationship between urinary sodium excretion and pioglitazone-induced edema. J Diabetes Investig 1: 208-211.

73. Jadoul M, Ferrant A, De Plaen JF, Crabbé J (1991) Mineralocorticoids in the management of primary adrenocortical insufficiency. J Endocrinol Invest 14: 87-91.

74. Rice SP, Agarwal N, Bolusani H, Newcombe R, Scanlon MF, et al. (2009) Effects of dehydroepiandrosterone replacement on vascular function in primary and secondary adrenal insufficiency: a randomized crossover trial. J Clin Endocrinol Metab 94: 1966-1972.

75. Srinivasan M, Irving BA, Dhatariya K, Klaus KA, Hartman SJ, et al. (2009) Effect of dehydroepiandrosterone replacement on lipoprotein profile in hypoadrenal women. J Clin Endocrinol Metab 94: 761-764.

76. Salem M, Tainsh RE Jr, Bromberg J, Loriaux DL, Chernow B (1994) Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. Ann Surg 219: 416-425.

77. Tohti M, Li J, Zhou Y, Hu Y, Yu Z, et al. (2015) Is peri-operative steroid replacement therapy necessary for the pituitary adenomas treated with surgery? A systematic review and meta analysis. PLoS One 10: e0119621.

78. Freedman BD, Kempna PB, Carlone DL, Shah MS, Guagliardo NA, et al. (2013) Adrenocortical zonation results from lineage conversion of differentiated zona glomerulosa cells. Dev Cell 26: 666-673.

79. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, et al. (1998) Embryonic stem cell lines derived from human blastocysts. Science 282: 1145-1147.

80. Kazutoshi Takahashi, Shinya Yamanaka (2006) Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. Cell 126: 663-676.

81. Seckl JR, Walker BR (2001) Minireview: 11beta-hydroxysteroid dehydrogenase type 1- a tissue-specific amplifier of glucocorticoid action. Endocrinology 142: 1371-1376.

82. Lindsay JR, Nieman LK (2005) The hypothalamic-pituitary-adrenal axis in pregnancy: challenges in disease detection and treatment. Endocr Rev 26: 775-799.

83. Cousins L, Rigg L, Hollingsworth D, Meis P, Halberg F, et al. (1983) Qualitative and quantitative assessment of the circadian rhythm of cortisol in pregnancy. Am J Obstet Gynecol 145: 411-416.

84. Mastorakos G, Ilias I (2003) Maternal and fetal hypothalamic-pituitary-adrenal axes during pregnancy and postpartum. Ann N Y Acad Sci 997: 136-149.

85. Scott EM, McGarrigle HH, Lachelin GC (1990) The increase in plasma and saliva cortisol levels in pregnancy is not due to the increase in corticosteroid-binding globulin levels. J Clin Endocrinol Metab 71: 639-644.

86. Waddell BJ (1993) The placenta as hypothalamus and pituitary: possible impact on maternal and fetal adrenal function. Reprod Fertil Dev 5: 479-497.

87. Räisänen I (1988) Plasma levels and diurnal variation of beta-endorphin, beta-lipotropin and corticotropin during pregnancy and early puerperium. Eur J Obstet Gynecol Reprod Biol 27: 13-20.

88. Odagiri E, Sherrell BJ, Mount CD, Nicholson WE, Orth DN (1979) Human placental immunoreactive corticotropin, lipotropin, and beta-endorphin: evidence for a common precursor. Proc Natl Acad Sci U S A 76: 2027-2031.

89. Janet S. Mackenzie, MD; Lara Burrows; Kenneth W. Burchard (1998) Transient Hypoadrenalism During Surgical Critical Illness FREE, Arch Surg 133: 199-204.

90. Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA, et al. (1987) A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 317: 653-658.

91. Baldwin WA, Allo M (1993) Occult hypoadrenalism in critically ill patients. Arch Surg 128: 673-676.

92. Anton I. Kidess, M.B., B.S., Robert H. Caplan, M.D.", Richard H. Reynertson, M.D.A, Gary G. Wickus, Ph.D. David E. Goodnough, M.D, Transient Corticotropin Deficiency in Critical Illness. doi: 10.1016/S0025-6196(12)60188-8

93. Jurney TH, Cockrell JL Jr, Lindberg JS, Lamiell JM, Wade CE (1987) Spectrum of serum cortisol response to ACTH in ICU patients. Correlation with degree of illness and mortality. Chest 92: 292-295.

94. Emedicine, medscape, euthyroid sick syndrome. emedicine.medscape.com/article/118651-overview \l "April 4/2014.

95. Wilson M, Morganti AA, Zervoudakis I, Letcher RL, Romney BM, et al. (1980) Blood pressure, the renin-aldosterone system and sex steroids throughout normal pregnancy. Am J Med 68: 97-104.

96. Xia Y, Pan M, Zhang Z (1996) [Addison's disease in pregnancy: a report of six cases]. Zhonghua Fu Chan Ke Za Zhi 31: 226-228.

97. Husebye ES, Allolio B, Arlt W, Badenhoop K, Bensing S, et al. (2014) Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. J Intern Med 275: 104-115.

98. Raber J, O'Shea RD, Bloom FE, Campbell IL (1997) Modulation of hypothalamic-pituitary-adrenal function by transgenic expression of interleukin-6 in the CNS of mice. J Neurosci 17: 9473-9480.