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EC MICROBIOLOGY
Review Article

Addison's Disease Diagnosis and Management

Sami Ahmed Bilal[1]*, Mohmed Salem Basalama[2], Saad Thamer A Alshahrani[3], Ageel Bati Alharbi[4], Sufyan Ahmad Alkhalaf[5], Fahad Saleem Alhawati[5], Ahmad Hamza Omar Khalid[6], Sultan Sameer Alhunbusi[7], Khalid Saleh Bamahfuth[8], Aqeela Ali Hasan Mohamed Sharif Alaradi[9], Haram Hafiz Osman Elhassan[10] and Ahmed Hamza Alnashri[11]

[1]Consultant of Internal Medicine, King Fahad General Hospital, Jeddah, Saudi Arabia

[2]King Fahad General Hospital, Jeddah, Saudi Arabia

[3]King Khalid University, Abha, Saudi Arabia

[4]Dammam Medical Complex-Eastern Province, Saudi Arabia

[5]King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

[6]King Faisal Medical Complex, Taif, Saudi Arabia

[7]King Abdul Aziz Specialist Hospital, Taif, Saudi Arabia

[8]King Abdulaziz University, Jeddah, Saudi Arabia

[9]Zhejiang University, China

[10]Bahri University, Sudan

[11]Umm Al-Qura University, Mecca, Saudi Arabia

***Corresponding Author:** Sami Ahmed Bilal, Consultant of Internal Medicine, King Fahad General Hospital, Jeddah, Saudi Arabia.

Received: June 14, 2019; **Published:** June 21, 2019

Abstract

Introduction: Recent research in the field of immunopathology has significantly enhanced our understanding of the concepts of autoimmune diseases, specifically of Addison's disease. Addison's disease is considered to be a chronic medical condition that is characterized by the presence of adrenocortical gland insufficiency that occurs after a chronic and often asymptomatic period, characterized by circulating autoantibodies which are directed to adrenal cortex antigens. In this review we will describe the categories of subjects who are at risk of having Addison's disease, as well as he diagnostic tests that are known to be the best for assessing the adrenal functions: the determination of basal plasma adrenocorticotropic hormone (ACTH) concentrations, the activity of plasma renin, plasma aldosterone and cortisol concentrations, and cortisol concentrations following IV stimulation with ACTH (known as ACTH test). The use of specific clinical, immunological and functional criteria in patients with autoantibodies to against the adrenal cortex makes it possible to identify those subjects who are at risk of having an overt disease. The independent risk factors for the development of adrenal failure contribute to different predisposing factors of developing clinical Addison's disease.

Based on the level of risk, patients must be strictly monitored over time to detect the presence of early signs of any adrenal dysfunction and start substitutive management as early as possible. For subjects who present with high risk, prophylactic strategies and trials may be beneficial.

Aim of Work: In this review, we will discuss Addison's disease.

Methodology: We did a systematic search for Addison's disease diagnosis and management using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

Conclusions: Primary adrenal insufficiency, also known as Addison disease, has many etiologies, the most common of which is a condition called autoimmune adre¬nalitis. Autoimmune adrenalitis is a result of the destruction of the adrenal cortex gland, which causes deficiencies in glucocor¬ticoids, mineralocorticoids, and adrenal androgens. In the US and Western Europe, the estimated prevalence of Addison disease is about in 20,000 persons; thus, a high clinical suspicion is required to prevent misdiagnosing a life-threatening adrenal crisis (like shock, hypotension, and volume depletion). Signs and symptoms prior to an adrenal crisis are subtle and could include hyperpigmentation, fatigue, anorexia, orthostasis, nausea, muscle and joint pain, and salt craving. Cortisol concentrations reduce and adrenocorticotropic hormone concentrations elevate. When clinically suspected, patients must undergo a cosyntropin stimulation test to confirm the presence of the disease. Management of primary adrenal insufficiency needs replacement of mineralocorticoids and glucocorticoids. During times of stress (like illness, inva¬sive surgical procedures), stress-dose glucocorticoids are needed as the destruction of the adrenal glands prevents a sufficient physiologic response. Management of primary adrenal insufficiency or autoimmune adrenalitis needs vigilance for concomitant autoimmune diseases; up to half the patients will develop another autoimmune disorder during their lifetime.

Keywords: *Addison's Disease; Presentation; Diagnosis; Management*

Introduction

Recent research in the field of immunopathology has significantly enhanced our understanding of the concepts of autoimmune diseases, specifically of Addison's disease. Addison's disease is considered to be a chronic medical condition that is characterized by the presence of adrenocortical gland insufficiency that occurs after a chronic and often asymptomatic period, characterized by circulating autoantibodies which are directed to adrenal cortex antigens. In this review we will describe the categories of subjects who are at risk of having Addison's disease, as well as he diagnostic tests that are known to be the best for assessing the adrenal functions: the determination of basal plasma adrenocorticotropic hormone (ACTH) concentrations, the activity of plasma renin, plasma aldosterone and cortisol concentrations, and cortisol concentrations following IV stimulation with ACTH (known as ACTH test). The use of specific clinical, immunological and functional criteria in patients with autoantibodies to against the adrenal cortex makes it possible to identify those subjects who are at risk of having an overt disease. The independent risk factors for the development of adrenal failure contribute to different predisposing factors of developing clinical Addison's disease.

Based on the level of risk, patients must be strictly monitored over time to detect the presence of early signs of any adrenal dysfunction and start substitutive management as early as possible. For subjects who present with high risk, prophylactic strategies and trials may be beneficial.

In this review, we will discuss the most recent evidence regarding Addison disease diagnosis and management.

Methodology

We did a systematic search for Addison's disease diagnosis and management using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: Addison's disease, presentation, diagnosis, management.

Adrenal cortex and 21-hydroxylase autoantibodies in patients with Addison's disease

Adrenal cortex autoantibodies (ACA) were first discovered in the year 1963 using the indirect immunofluorescence technique on the cryostat sections of animal models of adrenal glands [1]. Adrenal cortex autoantibodies reacted with a microsomal antigen which is common to the whole 3 layers of the adrenal cortex gland, producing a pattern that is homogenous cytoplasm-staining. Later, and in the period between 1963 and 2002, the use of the indirect immunofluorescence technique (IFT) on animal or human models with normal adrenal cryostat functions was the only available method for the detection of Adrenal cortex autoantibodies, which were found in up to sixty-one percent of autoimmune Addison's disease patients who were evaluated with different disease duration and in 6.7 percent of tuberculosis-related Addison's disease patients [2].

In the year 1992 it was found that the enzyme 21-hydroxylase (21-OH) is the main autoantigen that is recognized by Adrenal cortex autoantibodies. Later, an immunoprecipitation assay using 35 S-methionine-labelled 21-OH was introduced into the laboratory practice to find 21-OH autoantibodies (21-OH-Ab). then, a better method to evaluate 21-OH-Ab levels based on 125 I-labelled recombinant human 21-OH was created and made available as a kit [3]. Using special immunoprecipitation assays, 21-OH-Ab were detected in more than ninety percent of patients who had recent-onset autoimmune Addison's disease [4], but in none with other forms of Addison's disease. Autoantibodies reactive with the adrenal cortex with characteristics that are different to Adrenal cortex autoantibodies were later detected in IFT [5]. These autoantibodies, unlike adrenal specific Adrenal cortex autoantibodies, also demonstrated reactivity to the ovaries, testes as well as the placenta, and were known as steroid-producing cell autoantibodies. The specific antigens demonstrated by steroid-producing cell autoantibodies are steroid-producing enzymes, 17α-hydroxylase and the cytochrome p450 side-chain cleavage enzyme [6]. Steroid-producing cell autoantibodies are present in a large number of patients with Addison's disease (thirty-four percent) and in ninety-two percent of females with premature ovarian failure of less than five years' duration. Autoantibodies to steroidogenic enzymes could be predictive markers of premature ovarian failure, while ACA/21-OH-Ab are strictly adrenal cortex specific and are markers of autoimmune Addison's disease.

Is progression to Addison's disease mandatory?

The progression to an Addison's disease case in patients with positive autoantibodies is usually variable and not mandatory as only a certain proportion of these individuals will develop a clinical case. The clinical onset occurs usually within ten-to-eleven years following the first detection of Adrenal cortex autoantibodies, and almost never after longer than this period.

A previous study that followed-up 148 patients with ACA/21-OH-Ab positivity for a mean period of about six years (range: two months to twenty-seven years) found that the cumulative risk of developing overt Addison's disease at eleven years is about thirty percent in this cohort of patients, but it is significantly higher in Adrenal cortex autoantibodies-positive patients with type 1 autoimmune polyglandular syndrome (up to seventy-eight percent) when compared to patients with other autoimmune associated diseases (twenty-two percent). ACA/21-OH-Ab-positive patients without clinical Addison's disease for whom more than eleven years of follow-up data were available extremely rarely developed clinical Addison's disease.

The natural history of Addison's disease is classically categorized in three phases: potential, subclinical and clinical. The point of no return for developing clinical Addison's disease has been defined as a stage 1; when renin activity becomes higher. In the subclinical phases of Addison's disease, any stress-related event (including trauma, infection, surgery, pregnancy or any other possible stress) needing an elevation in cortisol secretion might cause an acceleration of adrenocortical dysfunction.

Is it possible to predict the onset of clinical adrenal failure with more precision?

A previous study have attempted to detect the independent predicting factors for the progression to adrenal cortical dysfunction in individuals with positive ACA/21-OH-Ab [7] and used a multivariate analysis to analyze a number of clinical, biochemical and immunological factors at the start of the follow-up of ACA/21-OH-Ab-positive subjects: (1) age, (2) sex, (3) concentrations of ACA/21-OH-Ab, (4) the status of adrenal function, (5) the presence of class II HLA haplotype and (6) type of preexisting autoimmune condition. The study demonstrated that the development of clinical Addison's disease was correlated with 4 independent factors: (1) sex (men compared to women, $p < 0.001$), (2) the type of comorbid autoimmune diseases (chronic hypoparathyroidism and/or mucocutaneous candidiasis

compared to thyroid autoimmune disease and/or type one diabetes mellitus, p = 0.009), (3) ACA/21-OH-Ab concentrations (high concentrations compared to medium-low concentrations, p = 0.02) and (4) the status of adrenal function (impaired compared to normal adrenal function, p < 0.0001).

Using these findings, individuals' risk of developing Addison's disease could be scored based on their risk factors. The risk for clinical Addison's disease was considered relatively low when the score was < 0.10, moderate when the score ranged between 0.10 and 0.40, and high when the score is larger 0.40. The scoring system for Addison's disease risk might have two practical outcomes: (1) it could assess the time intervals for performing biochemical tests based on risk level, and (2) it could aid in the selection of patients for recruitment to immune-intervention studies aimed at preventing the occurrence of Addison's disease.

Diagnosis

Metabolic tests

The target of laboratory investigations is to detect the presence of a low cortisol concentrations and assess if the cause of adrenal insufficiency is primary or secondary. Low serum cortisol concentrations at eight a.m (less than three mcg per dL [eighty-three nmol per Liter]) indicates the presence of adrenal insufficiency, as do low serum sodium and high serum potassium concentrations [8]. Hyponatremia could be caused by cortisol and mineralocorticoid deficiencies, where on the other hand, hyperkalemia is caused solely by a decrease of mineralocorticoids concentration.

As adrenal hormones are gradually lost over years, the concentrations vary. One of the main indications of the presence of an adrenal cortex malfunction is a high plasma renin concentrations [9]. An increase in ACTH concentrations is concomitant with the decrease of adrenal hormones. Continuous Yearly monitoring of ACTH concentrations in at-risk individuals demonstrates that measurements higher than fifty pg per mL (eleven pmol per Liter), which exceed the upper limit of normal, are suggestive of cortisol deficiency. A cosyntropin stimulation test is the first-line investigation for the diagnosis of adrenal insufficiency. The serum cortisol, plasma ACTH, plasma aldosterone, and plasma renin concentrations must be measured before giving 250 mcg of ACTH. At thirty and sixty minutes following the administration of IV ACTH, the serum cortisol concentration must be measured again. A normal response develops with peak cortisol concentrations higher than eighteen to twenty mcg per dL (497 to 552 nmol per L); a less or absent response is diagnostic for adrenal insufficiency [10].

Immunologic tests

The measurement of 21-hydroxylase antibody concentrations aid discerns the cause of Addison disease. The 21-hydroxylase enzyme is important for the synthesis of cortisol in the adrenal cortex gland; antibodies directed against the enzyme are specific for autoimmune adrenalitis and can be detected before the onset of clinical manifestations.

Imaging

Radiographic imaging is also another helpful technique for the determination of the cause of Addison disease, but it is somewhat nonspecific in patients with autoimmune destruction. It is, thus, important to make a biochemical diagnosis of adrenal insufficiency prior to radiographic imaging. Computed tomography shows small adrenal glands in patients who have autoimmune adrenal gland destruction. In other etiologies of Addison disease, computed tomography might demonstrate hemorrhage, calcification associated with tuberculosis infection, or masses in the adrenal gland itself. On the other hand, computed tomography is not needed to confirm the diagnosis of adrenal gland insufficiency.

Treatment

Hormone therapy

Management of Addison disease consists of lifelong hormonal therapy with glucocorticoids and mineralocorticoids16. Until now, there is no therapy available to prevent the underlying immune destruction of the adrenal cortex gland. usually, glucocorticoid replacement

includes using oral prednisone or hydrocortisone [11]. Prednisone could be taken once a day, while hydrocortisone is divided into 2 or 3 doses everyday. Mineralocorticoids are usually replaced with fludrocortisone at a dose that is sufficient to keep the plasma renin concentrations in the upper limit of the normal range. males who have Addison disease do not require replacement with androgens because their testes are able to secrete sufficient testosterone concentrations; on the other hand, females could benefit from the use of androgen replacement as the adrenal glands are the main source of androgen production and secretion in females. A previous meta-analysis of ten randomized controlled trials concluded that the use of dehydroepiandrosterone (DHEA) supplementation led to a small improvement in health-related quality of life and depression in females who had adrenal insufficiency [12].

Stress dosing of glucocorticoids

Patients must be counseled about the need for stress-dose glucocorticoids for medical conditions and prior to surgical operations because the destruction of the adrenal glands prevents the development of a sufficient physiological response to stress. There are several experts' guidelines for stress dosing of steroids which are based on the degree of stress; clinical trials that compared different approaches are not sufficient in the literature. In clinical practice, a stress-dose strategy for outpatient procedures (including colonoscopy, upper endoscopy) and invasive dental procedures (including root canal) that patients could apply easily is generally used. This includes a dose of glucocorticoids 3 times the maintenance dose on the same day of the procedure and 2 days following the procedure (like 3 times 3 rule for stress-dose glucocorticoids).

For minor medical conditions like influenza or viral gastroenteritis, the patient could take 3 times the steroid dose during the condition and continue normal dosing following the resolution of clinical manifestations. Patients must also have an injectable formula of glucocorticoid (intramuscular dexamethasone) present for cases of nausea, vomiting, or other conditions where oral intake is not possible. Mineralocorticoid replacement usually does not need to be altered for medical conditions or procedures. On the other hand, the dose might require to be modified in the months of the summer season when there are higher rates of salt loss from excessive perspiration.

Treatment caveats

Thyroid hormonal treatment in individuals who have undiagnosed Addison disease might predispose the development of an adrenal crisis because the thyroid hormone elevates the hepatic excretion of cortisol. Additionally, patients with a new diagnosis could have a reversible elevation in thyroid-stimulating hormone concentrations as glucocorticoids prevent secretion [13]. Glucocorticoid replacement could lead to normalization of the thyroid-stimulating hormone concentrations less than thirty mIU per Liter. In persons with type one diabetes mellitus, unexplained hypoglycemia and reduced insulin requirements might be the initial manifestations of the development of Addison disease [14].

Treatment of confirmed Addison disease

Patients who have Addison disease must be treated in conjunction with an endocrinologist and be strictly monitored regularly to guarantee appropriate hormone treatment. Glucocorticoid doses must be altered to the lowest tolerated concentration that controls clinical manifestations to decrease the adverse effects of excess glucocorticoid levels. It is essential to educate patients to learn the important guidelines for stress dosing of glucocorticoids, to have an injectable formula of glucocorticoid always available, and to wear an adrenal insufficiency medical alert sign.

It is estimate that about half the individuals who have Addison disease resulted by autoimmune adrenalitis will later develop another autoimmune disorder during their lifetime, making lifelong vigilance for associated autoimmune conditions an absolute necessity [15].

It is important to note that up to ten percent of females who have Addison disease will experience autoimmune premature ovarian failure, or primary ovarian insufficiency, during their reproductive years with the development of clinical manifestations of estrogen deficiency (like amenorrhea, flushing, fatigue, poor concentration). It is important to provide these patients with assessment and counseling on other options for building a family.

Conclusions

Primary adrenal insufficiency, also known as Addison disease, has many etiologies, the most common of which is a condition called autoimmune adrenalitis. Autoimmune adrenalitis is a result of the destruction of the adrenal cortex gland, which causes deficiencies in glucocorticoids, mineralocorticoids, and adrenal androgens. In the US and Western Europe, the estimated prevalence of Addison disease is about in 20,000 persons; thus, a high clinical suspicion is required to prevent misdiagnosing a life-threatening adrenal crisis (like shock, hypotension, and volume depletion). Signs and symptoms prior to an adrenal crisis are subtle and could include hyperpigmentation, fatigue, anorexia, orthostasis, nausea, muscle and joint pain, and salt craving. Cortisol concentrations reduce and adrenocorticotropic hormone concentrations elevate. When clinically suspected, patients must undergo a cosyntropin stimulation test to confirm the presence of the disease. Management of primary adrenal insufficiency needs replacement of mineralocorticoids and glucocorticoids. During times of stress (like illness, invasive surgical procedures), stress-dose glucocorticoids are needed as the destruction of the adrenal glands prevents a sufficient physiologic response. Management of primary adrenal insufficiency or autoimmune adrenalitis needs vigilance for concomitant autoimmune diseases; up to half the patients will develop another autoimmune disorder during their lifetime.

Bibliography

1. Blizzard RM and Kyle M. "Studies of the adrenal antigens and autoantibodies in Addison's disease". *Journal of Clinical Investigation* 42 (1963): 1653-1660.

2. Betterle C. "Addison's disease and autoimmune polyglandular syndromes". In Geenen V, Chrousos GP (eds): Immunoendocrinology in Health and Disease. New York, Marcel Dekker (2004).

3. Tanaka H., *et al*. "Autoimmune adrenal diseases - a new sensitive assay for measurement of steroid 21-hydroxylase autoantibodies". *Journal of Clinical Endocrinology and Metabolism* 82.5 (1997): 1440-1446.

4. Betterle C., *et al*. "Addison's disease: a survey on 633 patients in Padova". *European Journal of Endocrinology* 169.6 (2013): 773-84.

5. Anderson JR., *et al*. "Immunological features of idiopathic Addison's disease: an antibody to cell producing steroid hormones". *Clinical and Experimental Immunology* 3.2 (1968): 107-117.

6. Winqvist O., *et al*. "Identification of the main gonadal autoantigens in patients with adrenal insufficiency and associated ovarian failure". *Journal of Clinical Endocrinology and Metabolism* 80.5 (1995): 1717-1723.

7. Coco G., *et al*. "Estimated risk for developing autoimmune Addison's disease in patients with adrenal cortex autoantibodies". *Journal of Clinical Endocrinology and Metabolism* 91.5 (2006): 1637-1645.

8. Schmidt IL., *et al*. "Diagnosis of adrenal insufficiency: evaluation of the corticotropin-releasing hormone test and basal serum cortisol in comparison to the insulin tolerance test in patients with hypothalamic-pituitary-adrenal disease". *Journal of Clinical Endocrinology and Metabolism* 88.9 (2003): 4193-4198.

9. Betterle C., *et al*. "The natural history of adrenal function in autoimmune patients with adrenal autoantibodies". *Journal of Endocrinology* 117.3 (1988): 467-475.

10. Dickstein G., *et al*. "Adrenocorticotropin stimulation test: effects of basal cortisol level, time of day, and suggested new sensitive low dose test". *Journal of Clinical Endocrinology and Metabolism* 72.4 (1991): 773-778.

11. Crown A and Lightman S. "Why is the management of glucocorticoid deficiency still controversial: a review of the literature". *Clinical Endocrinology* 63.5 (2005): 483-492.

12. Alkatib AA., *et al*. "A systematic review and metaanalysis of randomized placebo-controlled trials of DHEA treatment effects on quality of life in women with adrenal insufficiency". *Journal of Clinical Endocrinology and Metabolism* 94.10 (2009): 3676-3681.

13. Kannan CR. "Diseases of the adrenal cortex". *Disease-a-Month* 34.10 (1988): 601-674.

14. Armstrong L and Bell PM. "Addison's disease presenting as reduced insulin requirement in insulin dependent diabetes". *British Medical Journal* 312.7046 (1996): 1601-1602.

15. Zelissen PM., *et al*. "Associated autoimmunity in Addison's disease". *Journal of Autoimmunity* 8.1 (1995): 121-130.

Volume 15 Issue 7 July 2019