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Overview of Pathogenesis and Treatment Options of Addison Disease

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Abstract: **Present study goal was to review the evidence about pathogenesis, diagnosis, and treatment approaches for Addison disease or as its also called primary adrenal insufficiency. PubMed, Medline, and Embase databases were comprehensively searched for relevant articles reporting Addison disease treatment options, pathogenesis and other different clinical aspects concerning this disease, with human subjects and only articles published in English language up to December, 2016. The cutaneous manifestations include darkening of the skin especially in sun-exposed areas and hyperpigmentation of the palmar creases, frictional surfaces, vermilion boundary, current marks, genital skin, as well as oral mucosa. The 250 µg ACTH stimulation examination supplies the medical diagnosis of adrenal insufficiency in the majority of patients. Dimension of totally free lotion or salivary cortisol could be useful when CBG is reduced, yet calls for standardization. Adrenal deficiency is connected with lowered lifestyle that may be caused by non-physiological glucocorticoid substitute.**

Keywords: **pathogenesis, diagnosis, treatment, frictional surfaces, vermilion boundary, genital skin.**

1. INTRODUCTION

Addison disease, or primary adrenal insufficiency, is a chronic condition of the adrenal cortex leading to poor manufacturing of glucocorticoid and also mineralocorticoid [(1)]. It is a relatively rare disease with a frequency of regarding 140 per million and an annual occurrence regarding 4 each million in Western populaces [(2)]. Addison disease is a possibly deadly problem if left neglected, yet its medical diagnosis is frequently missed or postponed. The principal signs of primary adrenal deficiency are fatigue, decreased cravings, and weight loss, as well as many patients experience salt food craving as well as dizziness. One of the most characteristic scientific sign is hyperpigmentation of the skin, which is triggered by elevated adrenocorticotropic hormone (ACTH) degrees [(3)]. The development of the disease and also its discussion varies significantly between people, making the medical diagnosis an obstacle for the doctor. Many patients have symptoms for years prior to medical diagnosis, whereas others advance more really [(4)]. Most likely, several patients die undiagnosed [(1,4)]. When thought, the medical diagnosis is typically simple, based on the particular clinical features such as tiredness, weight loss, hypotension and hyperpigmentation, as well as electrolyte disturbances consisting of hyperkalaemia and also hyponatraemia. Serum cortisol is typically listed below the reference array, as well as ACTH is blatantly raised [(5,6)]. Low serum aldosterone degrees, raised plasma renin focus or task, and reduced dehydroepiandrosterone sulphate degrees can further verify the diagnosis. The presence of anti-21-hydroxylase antibodies is analysis for autoimmune etiology [(7,8)], whereas patients negative for these antibodies require work-up for various other

causes. Primary adrenal deficiencies is brought on by a variety of diseases which can be categorized as devastating, because of a developmental defect, or impaired steroidogenesis [5,10]. In autoimmune polyendocrinopathy syndrome type 2, Addison disease happens in association with type 1 diabetes mellitus or autoimmune thyroid disease. Various other autoimmune problems, such as primary gonadal failing, pernicious anemia, and also vitiligo additionally may be present. A number of infective representatives can influence the adrenal gland, causing adrenal failing. Tuberculosis continues to be one of the most typical reason for Addison disease around the world [3,6,7]. In addition, current research studies have shown that cured patients with Addison disease have an understanding of minimized health-related quality of life and continue to be in danger of sudden death [6].

Present study goal was to review the evidence about pathogenesis, diagnosis, and treatment approaches for Addison disease or as its also called primary adrenal insufficiency.

2. METHODOLOGY

PubMed, Medline, and Embase databases were comprehensively searched for relevant articles reporting Addison disease treatment options, pathogenesis and other different clinical aspects concerning this disease, with human subjects and only articles published in English language up to December, 2016.

3. RESULTS

- **Pathogenesis, causes and clinical findings of Addison disease:**

A range of pathological processes could trigger Addison's disease, which wased initially described by Thomas Addison [11,12]. The commonest reasons for Addison's disease are autoimmune and also consumption. A number of autoimmune processes could lead to adrenal deficiency impacting solely the adrenal glands or be part of a much more intricate inherited autoimmune polyglandular syndrome [12,13,14]. Tuberculosis is one of the most common root cause of Addison's disease in developing nations. Fungal infection, hemochromatosis, metastatic neoplasm, and X-linked adrenoleukodystrophy are various other root causes of Addison's disease [11,15]. Numerous detectives have actually located dysphagia, exhaustion, weight management and also hypotension, abdominal pain, throwing up, amenorrhea, as well as nausea or vomiting, breakable as well as slim nail, scanty body hair in Addison's disease, which is also existing in this study [13,14,15,16]. Psychiatric signs and symptoms such as state of mind disruptions, reduced inspiration, and habits modifications are regularly related to Addison's disease. According to Anglin et al., the etiology of neuropsychiatric symptoms associated with Addison's disease is unidentified, however may be related with the disturbances in the electrophysiological, electrolyte, and metabolic task. In this situation, favorable history of mood disturbances and actions changes is likewise present [17]. Sleep disturbances on periodic exacerbation exists in this instance, which is according to the study by Løvås et al [18] One of the hallmark signs of Addison's disease is cutaneous as well as mucosal hyperpigmentations associated with ACTH melanogenesis activity [13,14,15]. Soule reported that today functions amongst 50 patients seen over a 17-year duration, as consisting of hyperpigmentation (86%), weight-loss (67%), abdominal pain (20%), and also looseness of the bowels (16%). Pigmentation can be blotchy or homogeneous. The pigmentation might involve skin, mouth, conjunctiva, as well as genitalia (**Figure 1**) [12,15]. Brown spots of gingival, vermillion border of the lips, buccal mucosa, taste, and also tongue could stand for the initial indications of Addison's disease [15].

Autoimmune adrenalitis in Addison disease can be divided into phases of development (**Table 1**) [2,19]. As the disease establishes, individuals shed adrenocortical function over a duration of years. In the first three phases, the human leukocyte antigen genetics provide hereditary risk; an unknown speeding up occasion launches antiadrenal autoimmunity; and also 21-hydroxylase antibodies are generated, which predict future disease. The production of these antibodies can come before signs and symptom onset by years to decades, and also they are present in greater than 90% of recent-onset instances [2,8]. In the fourth phase, obvious adrenal lack creates. One of the initial metabolic problems to happen is an increase in plasma renin degree, followed by the sequential development of various other irregularities, including a decreased reaction to adrenocorticotropic hormonal agent (ACTH) stimulation in the 5th stage.

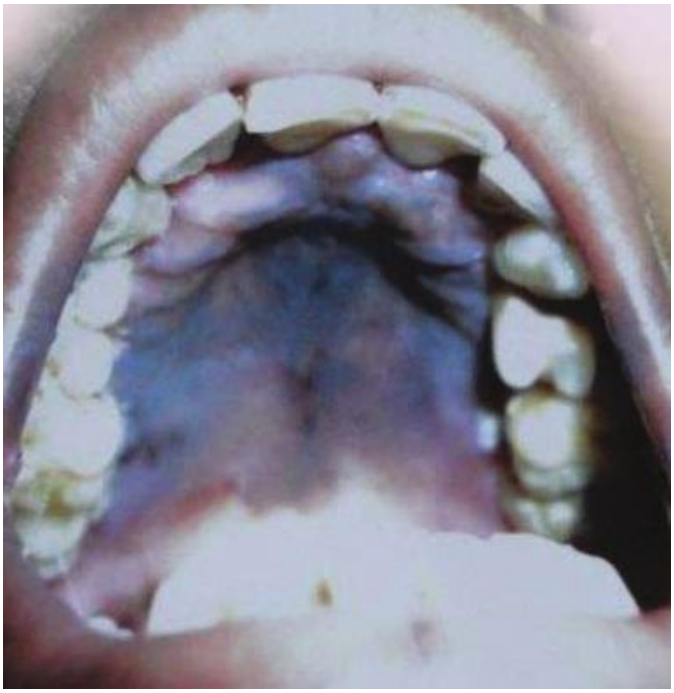

Figure 1: Hyperpigmentation in the palate

Table 1: Development Stages of Autoimmune Addison disease [2,19]

STAGE	SYMPTOMS	COMMENTS
1. Genetic risk	None	*HLA*-B8, -DR3, and -DR4 genes confer risk
2. Precipitating event starts antiadrenal autoimmunity	None	Possible environmental trigger
3. 21-hydroxylase antibodies present	None	Antibodies appear before disease onset in 90% of cases
4. Metabolic decompensation	Fatigue, anorexia, nausea, hyperpigmentation	Increased ACTH and decreased 8 a.m. cortisol levels; high clinical suspicion needed for diagnosis
5. Decreased response to ACTH stimulation	Hypotension and shock (addisonian crisis)	Severe symptoms can be life-threatening

Cutaneous symptoms of Addison's disease Darkening of the skin, particularly in the sun-exposed areas, is a characteristic indicator of primary adrenal deficiency (**Figure 1**) [2,15]. This hyperpigmentation may be blotchy or uniform as well as occurs in all racial and also ethnic groups, although it could be more difficult to discern in extremely dark-skinned individuals.14 In addition, isolated darker locations happen at the palmar creases, flexural locations, sites of friction, recent scars, vermilion boundary of the lips, and genital skin. It is necessary to identify that enhanced pigmentation of the palmar creases might be regular in darker skinned people. For this reason, comparison with various other family members and also the visibility or absence of added abnormal pigmentation ought to be taken into consideration when assessing this indication [16,17].

In primary Adrenal lack, there is failing of production of all hormones from the adrenal cortex; it is most often brought on by autoimmune damage in established nations [2,3] (**Table 1**). AI could take place alone, with various other autoimmune diseases (polyglandular autoimmune syndrome type 2 and also polygenic inheritance) or with hypoparathyroidism as well as mucocutaneous candidiasis (polyglandular autoimmune syndrome type 1) because of autosomal recessive inheritance of mutations in the AIRE gene [13].

Table 1: Causes of primary adrenal insufficiency

Cause	Prevalence (if known)
Autoimmune destruction	1 in 10,000
Congenital adrenal hyperplasia	1 in 15,000
X-linked adrenoleukodystrophy	1 in 20,000 men
Drugs inhibiting steroidogenesis	
Infectious	
Hemorrhagic	

- **Diagnostic procedures and treatment of Addison disease:**

Typically, Addison disease is diagnosed biochemically by measuring lotion cortisol before as well as 30, 45 and/or 60 minutes after intravenous administration of 250μg synthetic ACTH. Any value ≥ 18μg/ dl generally specifies a regular reaction [20]. This test can identify secondary adrenal insufficiency (AI) arising from not enough endogenous ACTH, which ultimately results in adrenal atrophy and also a reduced cortisol response. ACTH excitement testing ought to not be made use of before adrenal atrophy has happened (e.g. after recent pituitary surgical treatment). It has actually been suggested that ACTH excitement screening might also do not have level of sensitivity in chronic secondary adrenal lack, due to the fact that it accomplishes supra-physiological degrees of ACTH. Rather, a 1μg dosage was suggested and at first was reported to do likewise to the 250μg test [21]. In 2008, Kazluaskaite et alia, [22] reported that the 1μg examination was superior based on a meta-analysis of 679 patients with suspected additional adrenal lack, utilizing a cortisol analysis limit of 16μg/ dl [22]. However, as Stewart as well as Clarke explain in their feedback letter, this prevalence needed exemption of 5 research studies that utilized a fluorescence immunoassay, with adjustment of plasma cortisol values to their anticipated serum worths, thus decreasing its generalizability [23].

If a cortisol requirement of 18 μg/ dl is used, considerable proportions of healthy and balanced children [24] as well as adults [25,26] stop working the 1 μg test. This may be discussed partly by incomplete shipment of the dose [25]. Such reduced uniqueness might lead to unneeded long-lasting glucocorticoid substitute. Moreover, there is even more experience regarding limited test responses to the 250μg dose [23]. The 10% of overall lotion cortisol not bound to corticosteroid binding globulin (CBG) is thought to be naturally active, so measurement of this free portion might better mirror underlying cortisol physiology [27]. In a current research study, salivary (totally free) cortisol executed similarly however not better than product (total) cortisol throughout a 250 μg ACTH-stimulation test in patients with secondary Addison disease [28]. If totally free lotion as well as salivary cortisol assays come to be a lot more extensively available and defined, they may confirm handy, especially in patients with uncommon CBG focus.

4. CONCLUSION

The cutaneous manifestations include darkening of the skin especially in sun-exposed areas and hyperpigmentation of the palmar creases, frictional surfaces, vermilion boundary, current marks, genital skin, as well as oral mucosa. The 250 μg ACTH stimulation examination supplies the medical diagnosis of adrenal insufficiency in the majority of patients. Dimension of totally free lotion or salivary cortisol could be useful when CBG is reduced, yet calls for standardization. Adrenal deficiency is connected with lowered lifestyle that may be caused by non-physiological glucocorticoid substitute.

REFERENCES

[1] Arlt W, Allolio B. Adrenal insufficiency. Lancet. 2003;361:1881- 1893.

[2] Erichsen MM, Lovas K, Skinningsrud B, et al. Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency: observations from a Norwegian Registry. J Clin Endocrinol Metab. 2009; 94:4882-4890.

[3] Betterle C, Dal Pra C, Mantero F et al. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. Endocrine Reviews 2002; 23: 327–364.

[4] Myhre AG, Undlien DE, Løvås K et al. Autoimmune adrenocortical failure in Norway autoantibodies and human leukocyte antigen class II associations related to clinical features. The Journal of Clinical Endocrinology and Metabolism 2002; 87: 618–623.

[5] Mason AS, Meade TW, Lee JA et al. Epidemiological and clinical picture of Addison's disease. Lancet 1968; 2: 744–747.

[6] Bergthorsdottir R, Leonsson-Zachrisson M, Oden A et al. Premature mortality in patients with Addison's disease: a population-based study. The Journal of Clinical Endocrinology and Metabolism 2006; 91: 4849–4853.

[7] Coco G, Dal Pra C, Presotto F et al. Estimated risk for developing autoimmune Addison's disease in patients with adrenal cortex autoantibodies. The Journal of Clinical Endocrinology and Metabolism 2006; 91: 1637–1645.

[8] Winqvist O, Karlsson FA & Ka¨mpe O. 21-Hydroxylase, a major autoantigen in idiopathic Addison's disease. Lancet 1992; 339: 1559–1562.

[9] Falorni A, Nikoshkov A, Laureti S et al. High diagnostic accuracy for idiopathic Addison's disease with a sensitive radiobinding assay for autoantibodies against recombinant human 21-hydroxylase. The Journal of Clinical Endocrinology and Metabolism 1995; 80: 2752–2755.

[10] Ten S, New M & Maclaren N. Clinical review 130: Addison's disease 2001. The Journal of Clinical Endocrinology and Metabolism 2001; 86: 2909–2922.

[11] Hiatt JR, Hiatt N. The conquest of Addison's disease. Am J Surg. 1997;174:280–3.

[12] Stewart PM, Krone NP. The adrenal cortex. In: Kronenburg HM, Melmed S, Polonsky KS, Reed Larson P, editors. Williams Textbook of Endocrinology. 12th ed. Philadelphia PA: Saunders Elsevier; 2011. pp. 515–20. Ch. 15.

[13] Zargar AH, Laway BA, Masoodi SR, Bashir MI, Wani AI, Salahuddin M. A critical evaluation of signs and symptoms in the diagnosis of Addison›s diseases. J Assoc Physicians India. 2001;49:523–6.

[14] Lanza A, Heulfe I, Perillo L, Dell'Ermo A, Cirillo N. Oral manifestation as a sign of Addison's disease: A brief reappraisal. Open Dermatol J. 2009;3:3–6.

[15] Ten S, New M, Maclaren N. Clinical review 130: Addison's disease 2001. J Clin Endocrinol Metab. 2001;86:2909–22.

[16] Soule S. Addison' disease in Africa: A teaching hospital experience. Clin Endocrinol (Oxf) 1999;50:115–20.

[17] Anglin RE, Rosebush PI, Mazurek MF. The neuropsychiatric profile of Addison's disease: Revisiting a forgotten phenomenon. J Neuropsychiatry Clin Neurosci. 2006;18:450–9.

[18] Løvås K, Husebye ES, Holsten F, Bjorvatn B. Sleep disturbances in patients with Addison's disease. Eur J Endocrinol. 2003;148:449–56.

[19] Eisenbarth GS, Gottlieb PA. Autoimmune polyendocrine syndromes. *N Engl J Med*. 2004;350(20):2068–2079.

[20] Speckart PF, Nicoloff JT, Bethune JE. Screening for adrenocortical insufficiency with cosyntropin (synthetic ACTH) Arch Intern Med. 1971;128:761–763.

[21] Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. Ann Intern Med. 2003;139:194–204.

[22] Kazlauskaite R, Evans AT, Villabona CV, et al. Corticotropin tests for hypothalamic-pituitary-adrenal insufficiency: a metaanalysis. J Clin Endocrinol Metab. 2008;93:4245–4253.

[23] Stewart PM, Clark PM. The low-dose corticotropin-stimulation test revisited: the less, the better? Nat Clin Pract Endocrinol Metab. 2009;5:68–69.

[24] Mushtaq T, Shakur F, Wales JK, Wright NP. Reliability of the low dose synacthen test in children undergoing pituitary function testing. J Pediatr Endocrinol Metab. 2008;21:1129–1132.

[25] Park YJ, Park KS, Kim JH, et al. Reproducibility of the cortisol response to stimulation with the low dose (1 microg) of ACTH. Clin Endocrinol (Oxf) 1999;51:153–158.

[26] Wade M, Baid S, Calis K, et al. Technical details influence the diagnostic accuracy of the 1 microg ACTH stimulation test. Eur J Endocrinol. 2010;162:109–113.

[27] Brien TG, Clerico A, Del Chicca MG, Zucchelli GC. The apparent free cortisol concentration and the free cortisol index: a comparative study. J Nucl Med Allied Sci. 1981;25:49–51.

[28] Deutschbein T, Unger N, Mann K, Petersenn S. Diagnosis of secondary adrenal insufficiency in patients with hypothalamic-pituitary disease: comparison between serum and salivary cortisol during the high-dose short synacthen test. Eur J Endocrinol. 2009;160:9–16.