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Addisons Disease: A Brief Review

Bathula Akanksha, Nagulapally Sanjana, Nelikanti Vaishnavi, Ashwini Vairale, Neha Ankireddy, Gayatri Devi Yasa*
CMR College of Pharmacy, Kandlakoya, Hyderabad -501401

Corresponding Author:
GAYATRI DEVI YASA
Assistant Professor,
Department of Pharmaceutical Chemistry,
CMR College of Pharmacy,
Kandlakoya, Medchal, Hyderabad, Telangana, INDIA - 501 401.

Abstract:- Addison's disease is a rare condition which occurs due to improper function or damage of the adrenal glands. The two outer layers of cells of the adrenal glands i.e. adrenal cortex are responsible for the production of several steroid hormones. Addison's disease, also known as primary adrenal insufficiency, result from the insufficient production of these two hormones, cortisol and aldosterone. These hormones help regulate metabolism, blood pressure and stress response. The absence of cortisol and aldosterone can affect almost every organ and tissue in the body. The symptoms of Addison's disease can vary from one individual to another. Symptoms usually develop slowly over time leading to delay in the proper diagnosis. In rare cases, the symptoms of Addison's disease can develop rapidly causing a condition called acute adrenal failure.

Keywords:- *Adrenal Glands, Cortisol, Aldosterone, Primary Adrenal Insufficiency, Adrenal Failure.*

I. INTRODUCTION

Addison's disease, a form of developed primary adrenal insufficiency, arises when an autoimmune mechanism triggers the destruction of the adrenal glands, leading to a deficiency in crucial hormones. This condition, classified as an uncommon but potentially life-threatening emergency, is specifically termed Addison disease when autoimmune processes result in primary adrenal insufficiency.

The adrenal glands play a pivotal role in producing hormones essential for various physiological functions. In Addison's disease, the autoimmune assault results in the loss of both adrenal cortexes, leading to a reduction in adrenocortical hormones such as cortisol, aldosterone, and androgens. This hormonal deficit is a hallmark of the disorder and underscores the complexity of its clinical manifestations.

Typically, the initial symptom of Addison disease is the deficiency in glucocorticoids, primarily cortisol. This deficit may manifest gradually, allowing for a slow progression of symptoms. However, in some cases, Addison's disease can also present acutely, often precipitated by other concurrent illnesses or stressors. The gradual increase in mineralocorticoid levels is characteristic of the disorder, further contributing to the clinical picture.

The manifestation and severity of adrenal insufficiency in Addison's disease are contingent upon the extent and rate of adrenal function involvement. The clinical presentation can vary widely, ranging from subtle symptoms to acute and potentially life-threatening emergencies. Understanding the nuanced nature of Addison's disease is crucial for prompt diagnosis and intervention, as the timely management of this condition can significantly impact patient outcomes.

II. ETIOLOGY

Adrenal insufficiency is a disorder that can be either primary or secondary and is defined by the adrenal cortices' incapacity to generate enough amounts of adrenocortical hormones. Primary adrenal insufficiency: also referred to as Addison's disease, primary adrenal insufficiency can result from any condition that directly damages the adrenal cortex.

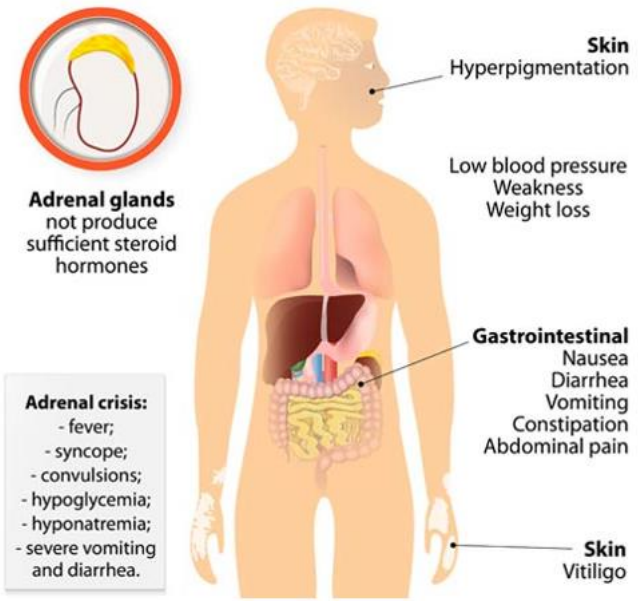

Fig1: Etiology of Addison's disease

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➢ *Causes of Autoimmune diseases:*

Autoimmune polyglandular endocrinopathies (types 1 and 2) are often responsible for the autoimmune destruction of adrenal glands, which frequently leads to Addison's disease.

Addison's illness, mucocutaneous candidiasis, and hypoparathyroidism are characteristics of type 1 autoimmune polyglandular syndrome.

Type 1 diabetes, autoimmune thyroiditis, and other autoimmune diseases are linked to type 2 autoimmune polyglandular syndrome.

➢ *Infections:*

- Adrenal insufficiency can result from infections such as HIV, CMV, Sepsis, and Tuberculosis.
- HIV is now a prominent cause of of adrenal necrosis linked to adrenal insufficiency.

➢ *Hemorrhage in the adrenals:*

Meningococcemia, Trauma, Neoplastic processes, and disseminated intravascular coagulation (DIC) are among the disorders that can cause bilateral adrenal hemorrhages.

➢ *Intrusion:*

Adrenal infiltration can result from metastases, hemochromatosis, and amyloidosis.

➢ *Additional reasons:*

Sarcoidosis, lymphoma, unusual diseases such anti-phospholipid antibody syndrome and wol-man disease, and genetic disorders such as congenital adrenal hyperplasia. Substances: some medications, such as etomidate and ketoconazole, can cause adrenal insufficiency by preventing the production of cortisol.

The more prevalent type, known as secondary adrenal insufficiency, is brought on by the injection of exogenous steroids, which suppresses the production of adrenocorticotropic hormone. The loss of adrenocorticotropic hormone secretion is pituitary-dependent and results in a decrease in the synthesis of glucocorticoids. Aldosterone secretion and other mineralocorticoid secretions continue to be largely normal. Usually, symptoms appear when the steroid is stopped.

Basically, what primary adrenal insufficiency entails inherent malfunction of the adrenal glands, frequently caused by an autoimmune response, resulting in deficits in cortisol and aldosterone. Chronic glucocorticoid therapy is the main cause of secondary adrenal insufficiency, which leads to hypothalamic-pituitary dysfunction and cortisol shortage**.**

III. EPIDEMIOLOGY

Addison's disease, though considered rare, holds significant implications for individuals affected by this insidious endocrine disorder. With an incidence of merely 0.6 cases per 100,000 of the population annually, it stands as a medical rarity. However, the prevalence, reflecting the total number of individuals grappling with Addison's disease at any given time, presents a broader impact ranging from 4 to 11 cases per 100,000 of the population.

This condition, marked by adrenal insufficiency, predominantly makes its presence known in the adult population. The age of onset is notably concentrated within the span of 30 to 50 years, underscoring the significance of recognizing potential manifestations during this particular life stage. While the disease is comparatively uncommon, its potential consequences are far-reaching, necessitating a nuanced understanding of its epidemiological nuances.

A distinctive feature of Addison's disease is its propensity to exhibit a gender bias, with a clear inclination towards women. This predilection introduces an intriguing facet to the epidemiological landscape, prompting a closer examination of potential hormonal, genetic, or immunological factors that may contribute to this gender-specific prevalence. Understanding such nuances not only aids in the recognition of potential cases but also lays the groundwork for tailored interventions that consider gender-specific variables in the disease's clinical course.

The autoimmune variant of Addison's disease, constituting the majority of cases, brings forth a specific set of epidemiological intricacies. Individuals grappling with this autoimmune type face an increased risk, and the condition often emerges in the context of other autoimmune diseases. The intricate web of autoimmune connections includes Type I diabetes, hypoparathyroidism, hypopituitarism, pernicious anaemia, Graves' disease, chronic thyroiditis, dermatitis herpetiformis, vitiligo, and myasthenia gravis. These comorbidities unveil a complex interplay within the immune system, where self-directed attacks lead to the gradual destruction of the adrenal glands.

Understanding the web of interconnected autoimmune conditions is pivotal in unravelling the etiological mysteries surrounding Addison's disease. The recognition of specific risk factors becomes a beacon guiding healthcare professionals in the early detection and management of this condition. Individuals presenting with autoimmune diseases mentioned earlier should be subjected to vigilant monitoring, ensuring timely intervention to mitigate the progression towards Addison's disease.

The autoimmune predisposition in Addison's disease not only underscores the multifaceted nature of immune dysregulation but also emphasizes the need for a holistic approach in healthcare. An intricate understanding of the immune system's intricate dance allows for a proactive stance in identifying at-risk individuals. This nuanced awareness is pivotal, not just in the diagnosis of Addison's

disease but also in the broader context of autoimmune conditions, fostering a comprehensive approach to patient care.

The potential morbidity associated with delayed diagnosis in Addison's disease magnifies the importance of increased awareness among healthcare professionals. Continuous medical education programs, emphasizing the epidemiological patterns, risk factors, and clinical presentations of Addison's disease, are instrumental in sharpening the diagnostic acumen of clinicians. This heightened awareness serves as a bulwark against oversight, ensuring that individuals presenting with symptoms indicative of adrenal insufficiency are promptly recognized and afforded the timely intervention they require. The epidemiology of Addison's disease, while characterized by its rarity, unravels a tapestry of complexities. The interplay of age, gender, and autoimmune predisposition adds layers of intricacy to its clinical landscape. A comprehensive understanding of these epidemiological nuances not only facilitates early detection and intervention but also underscores the imperative of continuous medical education to equip healthcare professionals with the tools necessary to navigate the diagnostic challenges posed by this rare but impactful endocrine disorder.

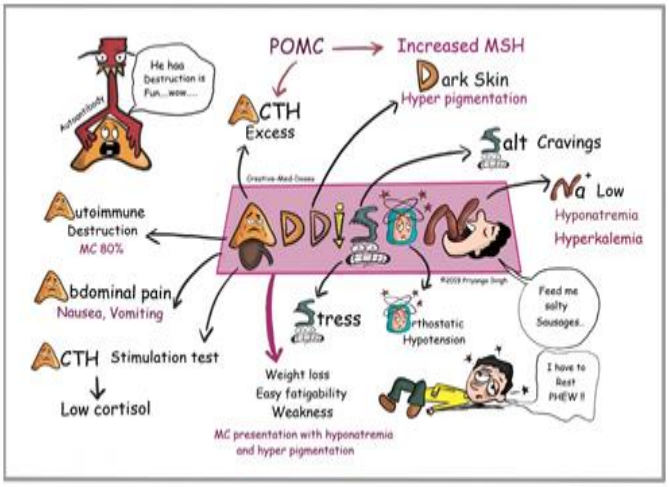

Fig 2: Addison's Disease: Visual Map

V. PATHOPHYSIOLOGY

Addison's disease, characterized by adrenal failure, manifests through a sequence of pathophysiological events that significantly impact hormonal regulation. The primary disruption begins with decreased cortisol production, a vital glucocorticoid hormone, which plays a crucial role in metabolic processes, immune function, and stress response. The adrenal glands, unable to produce sufficient cortisol, result in systemic consequences affecting energy metabolism, inflammation modulation, and the body's ability to cope with stress.

As cortisol levels decline, a subsequent impairment in aldosterone production occurs. Aldosterone, a mineralocorticoid, is responsible for maintaining electrolyte balance, particularly sodium and potassium, within the body. Its insufficiency leads to electrolyte imbalances, potentially causing hypotension, hyponatremia, and hyperkalemia.

The diminished cortisol and aldosterone production trigger a loss of negative feedback inhibition on the pituitary gland, prompting an elevation in adrenocorticotropic hormone (ACTH) and melanocyte-stimulating hormone (MSH). ACTH stimulates the adrenal cortex to produce more cortisol, attempting to compensate for the deficiency. However, the dysfunctional adrenal glands cannot respond adequately, exacerbating the hormonal imbalance.

Furthermore, increased MSH levels contribute to hyperpigmentation, a characteristic feature of Addison's disease. This occurs due to the structural similarity between ACTH and MSH, leading to the stimulation of melanocytes, resulting in darkening of the skin and mucous membranes.

The pathophysiology of Addison's disease involves a cascade of events starting with reduced cortisol and aldosterone, leading to electrolyte imbalances and hormonal dysregulation. The subsequent rise in ACTH and MSH reflects the body's attempt to compensate for adrenal insufficiency, ultimately contributing to the clinical manifestations observed in individuals with Addison's disease. Understanding these intricate mechanisms is essential for accurate diagnosis and effective management of this rare but potentially life-threatening condition.

VII. DIAGNOSIS

The differential diagnosis of adrenal crisis includes most other conditions that can cause shock. The differential diagnosis of adrenal insufficiency is broad. Some common differential diagnoses are discussed here.

- *Sepsis*

Many features of sepsis overlap with adrenal insufficiency. The presentation includes weakness, fatigue, vomiting, hypotension, and shock. The confirmation of primary adrenal insufficiency diagnosis is made by low cortisol response to ACTH stimulation test and low ACTH level.

- *Shock (due to any cause)*

Plasma cortisol level with shock suggests adrenal insufficiency.

- *Chronic Fatigue Syndrome*

Chronic persisting or relapsing fatigue may mimic adrenal insufficiency. However, laboratory evaluations such as cortisol level after corticotropin stimulation differentiate it from adrenal insufficiency.

- *Infectious Mononucleosis*

The presentation may be similar to fever, fatigue, and myalgias may occur in both conditions. However, exudative pharyngitis is present in this condition. IgM antibodies to viral capsid antigen are present.

➢ *Hypothyroidism*

As with adrenal insufficiency, fatigue may be present in hypothyroidism. However, it is associated with weight gain. The cortisol level should differentiate both conditions.

VIII. TREATMENT

Early recognition and intervention are crucial in managing adrenal insufficiency, with an adrenal crisis being a severe endocrine emergency that demands immediate attention to prevent fatal outcomes. The diagnostic process involves obtaining blood samples for subsequent measurement of ACTH and cortisol levels. An elevation of ACTH with low cortisol is indicative of primary adrenal insufficiency. In cases where the initial laboratory evaluation cannot establish the diagnosis, an ACTH stimulation test may be performed. Additionally, plasma renin levels are often elevated, indicating mineralocorticoid deficiency and a low aldosterone level.

➢ *Acute Phase:*

Patients in adrenal crisis require a multifaceted approach, including fluid resuscitation with intravenous (IV) normal saline to restore intravascular volume, dextrose administration to correct hypoglycaemia, and correction of hormone deficiencies, both glucocorticoid and mineralocorticoid. Hydrocortisone is the immediate hormonal treatment, administered at an initial dose of 100 mg IV bolus, followed by 50 to 100 mg IV every 6 hours over 24 hours. In children, the dose is adjusted to 50 mg/m^2 (max: 100 mg) IV bolus, followed by 50 to 100 mg/m^2. Notably, mineralocorticoids such as fludrocortisone are unnecessary during this acute phase.

Dexamethasone 4-mg IV bolus can be considered in the emergency department when urgent steroid administration is required, as it has a longer duration of action and is less likely to interfere with cortisol assays. The initial fluid replacement involves a normal saline bolus followed by 5% glucose in isotonic saline to promptly address hypoglycaemia.

➢ *Maintenance Phase:*

Life-long treatment with hormonal replacement is imperative in the maintenance phase. The goal is to maintain physiologic levels of glucocorticoid and mineralocorticoid. The usual doses for glucocorticoid replacement include hydrocortisone (5 to 25 mg/day) or prednisone (3 to 5 mg/day), with adjustments made based on clinical response and normalization of electrolyte abnormalities. To minimize adverse effects, doses should be titrated to the lowest effective amount.

For mineralocorticoid replacement, fludrocortisone is administered at a dose ranging from 0.05 to 0.2 mg daily. The initial hydrocortisone dose for children is 8 mg/m^2/day orally, divided into 3 or 4 doses. Fludrocortisone dosage should be tailored to maintain the plasma renin level within the reference range.

Considering concurrent medications is essential when determining the glucocorticoid dose, as certain drugs can influence hepatic glucocorticoid metabolism. Dexamethasone is not recommended for maintenance treatment due to difficulties in dose titration and an increased risk of the Cushing effect.

➢ *Treatment Considerations:*

- During times of stress, such as fever or infection, patients with Addison's disease should increase their hydrocortisone dose to compensate for a potential stress response.
- A standard stress dose is typically 2-3 times the daily maintenance dose.
- Patients taking revamping require an increased dose of hydrocortisone due to its impact on hydrocortisone clearance.
- Thyroid hormone can influence cortisol clearance, potentially precipitating an adrenal crisis. Glucocorticoid replacement may normalize thyroid-stimulating hormone.
- In patients with concomitant diabetes insipidus, glucocorticoid therapy may worsen the condition. Cortisol is necessary for free-water clearance, and cortisol deficiency can impact polyuria.
- Pregnancy, particularly in the third trimester, increases corticosteroid requirements.

In addition to these considerations, addressing underlying causes, such as sepsis, and managing associated conditions are critical for optimal outcomes in patients with Addison's disease. The collaborative efforts of an interprofessional healthcare team, including physicians, nurses, pharmacists, endocrinologists, and intensivists, contribute to the comprehensive care required for individuals with this condition.

➢ *Toxicity and Adverse Effect Management:*

Recognizing the urgency of Addison's disease treatment is paramount, as any delay may result in severe consequences, significantly increasing the rates of morbidity and mortality. The cornerstone of management involves the lifelong replacement of glucocorticoids and mineralocorticoids. Achieving and maintaining a delicate balance in their administration is crucial to prevent over- or under-treatment, both of which can lead to detrimental effects.

➢ *Prognosis:*

The treatment regimen for Addison's disease necessitates a meticulous approach to avoid adverse outcomes. The lifelong replacement of glucocorticoids and mineralocorticoids requires a strict balance, with careful monitoring to ensure optimal therapeutic effects and mitigate the risk of complications. Over-treatment with glucocorticoids can contribute to obesity, diabetes, and osteoporosis, while excessive mineralocorticoid replacement may induce hypertension. Moreover, individuals with Addison's disease face an increased susceptibility to developing other autoimmune conditions, with up to 50% potentially encountering additional autoimmune disorders.

Importantly, the introduction of thyroid hormone replacement in unrecognized patients can precipitate an adrenal crisis, emphasizing the need for thorough patient assessment and management strategies.

➢ *Complications:*

Failure to promptly recognize and treat Addison's disease can lead to the development of an adrenal crisis, marked by hypotension, shock, hypoglycaemia, acute cardiovascular decompensation, and potentially fatal outcomes. Beyond the immediate crisis, patients with adrenal insufficiency are at a heightened risk of death from infections, cancer, and cardiovascular causes. Delayed recognition and treatment of hypoglycaemia can also result in neurologic consequences. The administration of supraphysiologic glucocorticoid replacement poses the risk of Cushing syndrome, a condition with its own set of complications. In children, growth suppression may occur, impacting their overall development. Additionally, up to 10% of women with Addison's disease may experience premature ovarian failure or primary ovarian insufficiency, further highlighting the multifaceted nature of the complications associated with this condition.

➢ *Consultations:*

Optimal management of Addison's disease necessitates collaboration with healthcare specialists, particularly endocrinologists. In cases of an adrenal crisis, immediate consultation with intensivists is vital, and patients should be promptly admitted to an intensive care unit (ICU) for comprehensive care. This is especially crucial for those who appear ill and present with shock, requiring intensive monitoring and intervention to stabilize their condition.

➢ *Other Issues:*

- Idiopathic autoimmune adrenocortical insufficiency is the most common cause of Addison disease.
- Symptoms of Addison disease can be non-specific and, therefore, can be difficult to recognize. A high index of suspicion is required to make this diagnosis.
- Plasma cortisol < 3 mcg/dL at 8 with a simultaneous elevation of the plasma ACTH level >200 pg/mL establishes the diagnosis.
- Primary adrenal insufficiency diagnosis should be considered in acutely ill patients presenting volume depletion, hypotension, hyponatremia, and hyperkalaemia.
- It is important to consider the possibility of adrenal insufficiency in critically ill patients who failed to improve with resuscitation with fluid administration, particularly in the presence of hyperpigmentation, hyponatremia, or hyperkalaemia.
- In an Addisonian crisis, treatment is a priority and should not be delayed for diagnostic confirmation; a delayed treatment can be fatal.
- The treatment of choice for adrenal crisis is hydrocortisone; this has both glucocorticoid and mineralocorticoid properties.
- Glucocorticoid doses should be increased in the presence of fever, infection, or other stresses.
- Titrate the glucocorticoid dose to the lowest possible dose, which can control symptoms and minimize the adverse effects.
- Thyroid hormone treatment can precipitate an adrenal crisis since the thyroid hormone can increase the hepatic clearance of cortisol.
- Serum cortisol, plasma ACTH, plasma aldosterone, and plasma renin levels should all be obtained before performing the ACTH stimulation test.
- Addison disease due to autoimmune adrenalitis can develop another autoimmune disorder.

➢ *Deterrence and Patient Education:*

Beyond immediate medical interventions, a key aspect of managing Addison's disease involves patient education and preventive measures. Patients should receive comprehensive education on medication doses, adherence to the treatment plan, and the importance of adjusting steroid replacement doses during stressful situations such as fever, surgery, or stress. Wearing an emergency medical alert bracelet is essential for ensuring prompt and accurate medical attention during emergencies. Additionally, patients should be empowered with self-care practices, including maintaining an adequate sodium intake in the diet and regularly monitoring weight and blood pressure. These proactive measures aim to enhance patient awareness, promote adherence to treatment plans, and foster active participation in their own healthcare.

In conclusion, the comprehensive management of Addison's disease encompasses not only medical interventions but also collaborative consultations, patient education, and proactive measures to prevent complications. A multidisciplinary approach ensures the best possible outcomes for individuals grappling with this complex and potentially life-threatening condition.

➢ *Enhancing Healthcare Team Outcomes:*

Addison's disease, being a life-threatening condition, demands a coordinated and efficient interprofessional healthcare team to ensure accurate diagnosis and prompt treatment. Delayed diagnosis not only increases morbidity and mortality but also underscores the critical role of a collaborative approach in managing this complex endocrine disorder. An effective interprofessional team for Addison's disease management typically includes an endocrinologist, an intensivist, an infectious disease specialist, and a pharmacist.

The endocrinologist serves as the primary specialist overseeing the diagnosis and management of Addison's disease. They play a crucial role in initiating appropriate hormone replacement therapy, ensuring a delicate balance between glucocorticoids and mineralocorticoids, and monitoring the patient's response to treatment. The expertise of an endocrinologist is essential in tailoring treatment plans to individual patient needs and addressing potential complications.

In the acute setting, an intensivist becomes a vital member of the team, especially during adrenal crises. Their focus is on stabilizing the patient, managing shock, and providing intensive care in an ICU setting. This collaboration is indispensable in preventing severe complications associated with an adrenal crisis, such as hypotension and cardiovascular decompensation.

In infectious disease specialists, the team gains expertise in managing infections that can pose significant risks to individuals with adrenal insufficiency. Infections, if not promptly identified and treated, can further exacerbate the precarious balance of hormones in patients with Addison's disease. Therefore, the infectious disease specialist contributes to the holistic care of these patients, addressing infectious complications promptly and effectively.

Pharmacists play a critical role in the healthcare team by ensuring accurate and appropriate medication management. They contribute to dosing adjustments, monitor for potential drug interactions, and educate patients on proper medication administration. Their expertise in pharmacology is invaluable in optimizing therapeutic outcomes and minimizing the risk of adverse effects associated with hormone replacement therapy.

Education is a cornerstone of managing chronic conditions like Addison's disease. The responsibility of educating patients spans across healthcare professionals, including physicians, nurses, and pharmacists. Patients need to be informed about the nature of their condition, the importance of medication adherence, and the signs and symptoms of adrenal crisis. Collaboratively, the healthcare team can ensure that patients are equipped with the knowledge to recognize warning signs, facilitating early intervention and prevention of complications.

Nurses, as integral members of the interprofessional team, play a multifaceted role in Addison's disease management. They administer treatments, closely monitor patients for any signs of deterioration, and provide timely updates to the broader healthcare team. Their close interaction with patients positions them to reinforce educational efforts, ensuring that patients comprehend and adhere to their treatment plans.

Once a diagnosis is established, outcomes depend on addressing the underlying cause and maintaining a vigilant approach to treatment. Any delay in initiating the necessary therapy can result in poor outcomes, underscoring the importance of the collaborative efforts of the healthcare team. Patient outcomes are significantly influenced by the collective expertise and coordinated efforts of the interprofessional team, reinforcing the importance of a comprehensive approach to Addison's disease management.

A critical aspect of managing Addison's disease is patient empowerment through education and proactive measures. All patients diagnosed with Addison's disease should be strongly encouraged to wear a medical alert bracelet, providing vital information in case of emergencies. Patients need to be educated about the signs and symptoms of an impending adrenal crisis, emphasizing the urgency of seeking medical attention if warning symptoms arise. Furthermore, patients should be instructed to contact their primary care provider promptly in the presence of any concerning symptoms.

In times of stress, such as fever or surgery, patients must be educated on the necessity to double their steroid replacement doses. This proactive approach aims to prevent adrenal crises during periods of increased physiological demand. Patient education should be a collaborative effort involving physicians, nurses, and pharmacists, ensuring that information is effectively communicated and understood.

The management of Addison's disease is an intricate process that requires the seamless collaboration of an interprofessional healthcare team. The expertise of an endocrinologist, intensivist, infectious disease specialist, pharmacist, and nurse, combined with patient education and empowerment, forms the foundation for optimal outcomes. The emphasis on timely diagnosis, comprehensive treatment, and proactive measures is essential in mitigating the risks associated with Addison's disease and improving the overall well-being of affected individuals.

IX. CONCLUSION

Addison's disease is a rare, potentially life-threatening condition with nonspecific symptoms, often leading to delayed diagnosis. Addison's disease is a condition characterized by the adrenal cortex's inability to produce enough glucocorticoids and mineralocorticoids. It is prevalent in Western societies, with 100-140 cases per million, and is more common in women. Autoimmunity accounts for 85% of diagnoses, with other causes including tuberculosis, adrenal haemorrhage, and genetic disorders. The common autoimmune form is characterized by 21-hydroxylase autoantibodies. Patients may present with vague symptoms or specific signs like salt-craving and hyperpigmentation. Diagnosis is made through a biochemical assessment of the glucocorticoid hypothalamus-pituitary-adrenal axis and mineralocorticoid function. Prompt diagnosis is crucial for early treatment and appropriate patient follow-up. It typically involves fatigue and electrolyte imbalance disorders, but specific diagnostic features like hyperpigmentation should raise suspicion. Patients can regain normal daily activities, but require lifelong follow-up and surveillance.

In order to make an early diagnosis and start therapy, it is critical that medical personnel are knowledgeable about the clinical characteristics of Addison's disease. We also emphasise the importance of a comprehensive physical examination and a complete clinical history when evaluating individuals who present with hyponatremia.

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