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INVESTIGATING THE UNDERLYING CAUSES AND NOVEL TREATMENT APPROACHES FOR HYPOADRENALISM; A COMPREHENSIVE ANALYSIS OF ADRENAL INSUFFICIENCY

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Abstract: The aim of this study was to investigate the underlying causes, and novel treatment approaches for hypoadrenalism

Materials and Methods; This retrospective study was carried out at the department of medicine and endocrinology, Hayatabad Medical Complex, Peshawar, Pakistan, from December 2021 to November 2022. The study included 770 patients with suspected adrenal insufficiency (AI) who visited the hospital during that period. Those individuals were included who had experienced suspected AI symptoms through an adrenocorticotrophic hormone (ACTH) stimulation test, or insulin tolerance test (ITT). A peak cortisol concentration of less than 500 nmol/L (18 g/dL) was defined as AI. Patients' medical records were retrospectively analyzed for data such as age, sex, laboratory examinations, and the presence of diseases like thyroid disease, rheumatic diseases, hypertension, diabetes, respiratory diseases, or osteoporosis. All the data was analyzed through SPSS Software. Groups were compared through the two-tailed test and data was represented in the form of standard deviation, number and percentage. P value less than 0.05 were considered significant.

Results; 770 individuals with suspected adrenal insufficiency came to the hospital and were enrolled for this study; out of which 183 (23.7%) were diagnosed with adrenal insufficiency. In this data, the number of females were n=124 (67.8%), while n=59 (32.2%) were males. The mean age was 65.65±14.42 years. Out of the 183 AI diagnosed patients, n=98 (53%) were on steroid treatment. After investigation of AI and the various types of steroids used for daily hormonal replacement therapy, our study found that hydrocortisone replacement therapy, which was given twice a day, was the most commonly used medication. The most prevalent underlying cause of adrenal insufficiency in our study was infectious diseases (70%).
Conclusion; from our study it was explored that infectious diseases is the most prevalent underlying cause of adrenal insufficiency that can be overcome by hormonal replacement therapy.

KEYWORDS, Adrenal insufficiency, Infectious disease, hormonal therapy

Introduction

The inadequate synthesis of steroid hormones produced by the adrenal glands results in the potentially fatal illness known as adrenal insufficiency (AI). Depending on the reason, it can be classified as primary, secondary, and or tertiary. Disease intrinsic to the cortex of the adrenals causes primary AI. The combined term for secondary and tertiary AI is central AI, and it is brought on by a disruption in the hypothalamic-pituitary axis that impairs corticotrophin action or production [1]. Primary adrenal insufficiency (PAI) is due to autoimmune disorders and can also be linked to other forms of endocrine disease (polyendocrine syndrome). Infections, bilateral infarction, metastases, hemorrhages, adrenalectomy, and genetic syndromes are all potential causes of PAI. Secondary adrenal insufficiency (SAI) and hypophysitis are primarily caused by tumors of the pituitary gland, ACTH deficiency, and increased use of immune checkpoint inhibitor drugs. Other causes include trauma resulting from surgery, infarction (like Sheehan's syndrome), or infections. AI is primarily caused by tertiary adrenal insufficiency, which can be triggered by long-term high-dose synthetic glucocorticoid therapy or selective opioid effects that lead to prolonged suppression of the hypothalamic-pituitary-adrenal axis [3]. Symptoms include overall weakness, weariness, anorexia, stomach discomfort, weight loss, hypotension in the feet, and salt cravings brought on by adrenal breakdown. Thomas Addison originally described it in 1855 [4]. Prior to 1949, the majority of patients passed away within two years of diagnosis, with an extremely poor survival rate [5]. On the other hand, cortisone was first synthesized in 1949. AI sufferers may now go about their daily lives normally thanks to cortisone therapy. However, the identification and management of AI is frequently postponed due to the vague nature of the disease's primary symptoms, which typically appear gradually [6]. Although the diagnostic process is not difficult, it requires careful consideration of multiple points and the exclusion of other diagnostic possibilities [7]. The current study aim was to determine the underlying causes and novel treatment approaches for hypoadrenalism.

Materials and method

This retrospective study was carried out at the Department of Medicine and Endocrinology of Hayatabad Medical Complex, Peshawar, Pakistan from December 2021 to November 2022. The study included 770 patients with suspected adrenal insufficiency who visited the hospital. Those individuals were included who had experienced suspected AI symptoms through ACTH stimulation test or ITT. A peak cortisol concentration of less than 500 nmol/L (18 g/dL) was defined as AI. In order to induce hypoglycemia for the ITT, intravenous insulin injections (0.2 to 0.5 U/kg) were administered. Serum cortisol levels were then measured every 30 minutes for a minimum of two hours. Patients' medical records were retrospectively analyzed for data such as age, sex, laboratory examinations, and the presence of diseases like thyroid disease, rheumatic disease, hypertension, diabetes, respiratory disease, and osteoporosis. Clinical symptoms were also noted during the test that took place. Before and after the diagnosis, a record of steroid medication, treatment type, drug concentrations, and daily dosage was taken. The frequency and origins of adrenal crisis and overlapping ailments were noted.

All the data was analyzed through SPSS Software. Groups were compared through the two-tailed test and data was represented in the form of standard deviation, number and percentage. P value less than 0.05 was considered significant.

Results

A total of 770 individual with suspected adrenal insufficiency that came to the hospital were enrolled for this study; out of which 180 (23.7 percent) diagnosed with AI. In this data, the number of females were n=124 (67.8%), while n=59 (32.2%) were males. The mean age was 65.65±14.42 years. The mean level of ACTH was 10.06±21.75 microgram/mL, and cortisol was 3.46±3.56 microgram/mL. Na+ was 133.59±7.34 mmol/L, K+ was 3.98±0.64, and glucose was 121.89±52.67 mg/dL. The most prevalent co-morbidity was Hypertension (n=94, 51.4%), followed by diabetes (n=62, 33.9 percent) and respiratory disease (n=35, 19.1 percent), as presented in **table 1.** We assessed the number of patients who had a relevant medication record; out of 183 participants, n=98 (53%) were on steroid treatment in which 86 (87.8%) used to take steroids orally, and twelve (12.2%) by injection. The most common purpose for the utilization of steroid medicine was disorders of the joints (n=46, 46.9%), presented in **Fig no (1).**

Treatment (Hormone replacement) for AI

After the investigation of AI in our study and the various types of steroids used for daily replacement therapy, the following data was collected; 31 (71%) individuals took hydrocortisone, prednisolone was used by 50 (27.3%) individuals, while 1 (0.5%) received both, and 1 (0.5%) was not receiving any treatment at the time. The maximum common daily prescription of a drug was 30 milligram of hydrocortisone. The majority of individuals (n=103, 78.6%) took hydrocortisone twice a day. Prednisolone was the second most utilized steroid of which 5 mg (n=17, 34.0%) was the most often administered daily dosage, followed by 7.5 mg (n=13, 26.0%). Prednisolone was taken once a day by the majority of patients (n=31, 62.0%) **(Table 2)**.

Underlying Causes of adrenal insufficiency and inter current illness

With the use of medical records, we calculated that, throughout the course of the research period, 14 patients (7.7%) received treatment for either an intercurrent illness (n = 4, 2.2%) or an adrenal crisis (n = 10, 5.5%). According to Table 5, the causes of adrenal crisis were infection (n = 7, 70.0%), medication discontinuation (n = 2, 20.0%), and severe sickness (n = 1, 10.0%). Four individuals (about forty percent) out of the ten with an adrenal disease passed away while receiving therapy. Of them, one had stopped taking prescription drugs, and three had an infectious disease. The reasons for the co-occurring disease were surgical stress (n=1, 25.0%), medication discontinuation (n=2, 50.0%), and infection (n=1, 25.0%) **(fig 2)**.

Discussion

According to this retrospective, cross-sectional investigation, 183 out of 771 individuals who were thought to have AI were diagnosed. The majority of patients were female, and all had central AI. The most typical sign was all-around weakness. Among the patients, half had previously used steroid treatment. The majority of patients received hydrocortisone replacement treatment. Adrenal crisis or concurrent disease was treated in about 7.7% of the patients. The rate of occurrence and frequency of chronic primary AI in Europe are, respectively, 93–144 cases for each million and 4.4–6.0 new cases per million people year [8]. Primary AI is less prevalent than central AI. 150 to 280 instances of secondary AI are thought to occur per million [9].

In our study, we diagnosed AI in about 25% of the patients who were subjected to a rapid ACTH stimulation test, or an ITT to exclude AI, and all these patients had central AI. Primary AI was absent in our sample. Patients in our study had an average age of 66.7 years with women being the predominant group. Cardiovascular disease is more prevalent among patients with AI [12]. The influence of cortisol on metabolism could be indicative of this association, as Rosmond and Bjorntorp

demostrated a correlation between pathological changes in the hypothalamic-pituitary-adrenal axis and cardiovascular disease, type 2 diabetes, and stroke [13]. Our study analyzed the frequency of hypertension, diabetes, respiratory disease, thyroid disease (hypertension), rheumatic disease and osteoporosis. While hypertension was prevalent in the general population, diabetes was more common among them [14]. Our data has shown that the studied patients with AI are more susceptible to cardiovascular disease. Besides these, respiratory and rheumatoid diseases were prevalent. The use of steroids for treating these diseases may indicate that glucocorticoids used to treat various diseases are a common cause of AI. Hydrocortisone replacement is the preferred option for AI because hydrocortisone tablets taken twice or thrice a day produce circulating levels of glucocorticase, which is similar to the physiological circadian-based serum cortisol exposure-time profile [15]. In AI, the recommended daily intake of hydrocortisone as a replacement therapy is 15 to 25 mg, and it is suggested twice per day [16]. Our study found that hydrocortisone replacement therapy, which was given twice a day, was the most commonly used medication. In spite of this, only 35 patients were treated with hydrocortisone. A total of 44 people received daily doses of 15 to 20 mg, while only 9% fell under this range. 30 mg was given to 2% of the group each day [17]. The adequacy of replacement therapy cannot be determined objectively, so physicians must rely on the patient's symptoms and signs and appropriately administer the appropriate dose of glucocorticoid replacement. Due to the lethal nature of AI, medical professionals must be educated on how to recognize its symptoms and initiate timely treatment. The common underlying cause of adrenal insufficiency in our study was infectious diseases and severe illness, which is similar to the findings of a previous study [18].

Limitations

Our research has several drawbacks. Initially, the study is retrospective and based on medical chart review. Information bias is a common issue among it. Another limitation is that the study was conducted at one center.

Conclusion; from our study it was explored that infectious diseases is the most prevalent underlying cause of adrenal insufficiency that can be overcome by hormonal replacement therapy.

Table 1. Demographic and Medical Features of Patients with Adrenal Insufficiency (N=183+-)

Features	Patients with AI n=183(%)
Age in years	65.65±14.42
Sex	
Male	n=59(32.2 %.)
Female	n=124 (67.8)
Hormones and electrolytes	**AVERAGE**
Sodium (mmol/L)	133.59 (±7.34)
Potassium (mmol/L)	3.98 (±0.64)
ACTH (pg/mL)	10.06 (±21.75)
Cortisol (µg/dL)	3.46 (±3.56)
Diseases	**Number (%)**
Hypertension	94 (51.4%)
Diabetes	62 (33.9%)
Respiratory	35 (19.1%)
Thyroid	34 (18.6%)
Rheumatic	22 (12.0%)
Osteoporosis	22 (12.0%)
Hyperlipidemia	21 (11.5%)
AI, adrenal insufficiency ACTH, adrenocorticotropic hormone	

Table 2. Hormone Replacement Therapy in Patients with Adrenal Insufficiency	
Variable	Individuals with AI(N=183)
Daily dosage of hydrocortisone in milligram	
5	1 (0.8)
7	1(0.8)
10	24(18.3)
15	17(13.0)
20	30(22.9)
30	58(44.2)
Daily quantity of hydrocortisone	
Two times per day	103 ((78.6)
Once a day	28(21.4)
Daily prescription of prednisolone in milligram	
2.5	1 (2)
5	17 (34)
7	13 (26)
10	10 (20)
15	6 (12)
20	3 (6)
Daily amount of prednisolone	
Two times a day	19(38)
One a day	31(62)

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