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Occult Adrenal Insufficiency in Patients with Chronic Renal Disease

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Abstract

Background: Addison's disease is a rare disorder of the adrenal cortex that leads to inadequate production of cortisol initially followed by aldosterone and androgens. Its manifestations are usually slow and non-specific with potential for life-threatening adrenal crisis following hypermetabolic demands (infection, trauma, surgery). **Patients:** Over the past 10 years, 19 CRD-patients were diagnosed with occult PAI in our center. **Results:** Unprovoked hypotension was the most common manifestations of occult PAI and was the unmasking event in 11 (58%). It was without significant cardiac and/or severe systemic sepsis and was refractory to isotonic saline infusions. Equal number of the remaining patients (n = 2) presented with persistent and inexplicable electrolytes abnormalities viz. 1) hyponatremia despite restricted oral fluid intake, lack of dehydration and massive fluid overload, as well as 2) hyperkalemia despite potassium-restricted diet, hyperkalemic drugs and adequate therapy with Furosemide and low-potassium dialysis-baths. On the other hand, similar proportions presented with unprovoked 3) progressive weight loss, decrease appetite and cachexia as well as 4) frequent hypoglycemic attacks. All patients were treated and were medically stable after 29 (2 - 60) months of follow up. Autoantibodies to 21-hydroxylase enzyme were positive in 16 (90%). At diagnosis, and subsequent follow up, only 7 patients (37%) had multi-endocrine dysfunction of whom 2 with type 1 and 5 with type 2. **Conclusion:** High index of suspicion should be exerted in diagnosis of PAI in patients with CRD, since its clinical picture is similar to CRD manifestations and complications. In those patients, confirmatory tests and specific management can save their lives.

Keywords

Addison's Disease, Autoimmune Adrenalitis, Chronic Renal Disease, Multiple

Endocrine Dysfunctions, Primary Adrenal Insufficiency

1. Introduction

Addison's disease (AD), is a rare disorder of the adrenal cortex with an annual incidence of 0.6 per 100,000 of the population [1]. It leads to inadequate production of cortisol initially followed by aldosterone and androgens. Its manifestations are usually slow and non-specific with weakness, fatigue, musculoskeletal pain, skin hyperpigmentation, weight loss, abdominal pain, depression, and anxiety. Hence diagnosis is frequently delayed leading to acute life-threatening adrenal crisis following hypermetabolic demands (infection, trauma, surgery) [2]. Addisonian crisis is a potentially life-threatening state with dehydration, life-threatening hyponatremia/hyperkalemia and shock, due to the central role of adrenal hormones in energy, salt, and fluid homeostasis [3]. AD results from (a) steroid-withdrawal after prolonged-use, (b) bilateral adrenalectomy, (c) diseases of pituitary/hypothalamic axis, (d) adrenal dysgenesis, (e) infiltrative destruction, and (f) autoimmune impairment in steroidogenesis [4]. Infiltrative destruction of adrenal gland is associated with (a) granulomatous diseases such as tuberculosis, histoplasmosis, sarcoidosis, (b) infections such as HIV, cytomegalovirus, fungus, (c) metastatic from lung and breast, (d) systemic amyloidosis and hemochromatosis, (e) hemorrhage (Waterhouse-Friderichsen syndrome associated with Warfarin and leukemia. On the other hand, progressive impairment in steroidogenesis is an acquired autoimmune adrenalitis that is associated with inherited (genetic) predisposition and is being referred to as primary adrenal insufficiency (PAI). At present, rapid-withdrawal of Corticosteroids is the most common secondary form of AD while autoimmune adrenalitis (PAI) and genetic enzyme defects are the being the most common primary ones in adults and children, respectively [5]. The prevalence of PAI is 82 - 144/million [5]. However, such data may underestimate the disease due to its vague, non-specific and gradual manifestations. Moreover, patients with chronic renal disease have (a) manifestations viz. hyponatremia, hyperkalemia, progressive asthenia, weight loss and hyperpigmentation as well as (b) complications viz. hypotension, psychosis and cachexia that mimic PAI. In this retrospective study, we report on our experience with such underestimated disorder in this patient population in an attempt to improve their morbidity and mortality.

2. Patients and Methods

A retrospective analysis was performed on patients with occult adrenal insufficiency who had received treatment and follow up for the past 10 years starting from 1st January 2013 till 31st December 2023. The study was conducted at Amiri renal center in Kuwait City. The center is a referral institution for patients with renal disease in the 2 major hospitals in Kuwait City and is a tertiary care unit

for the other hospitals in Kuwait.

2.1. Study Design

Patients were included if they had occult PAI in association with (a) age ≥ 14, (b) moderate to severe chronic renal disease, (b) stable heart and liver disease, (c) lack of previous Corticosteroid-use, (d) absence of manifestations of infective or infiltrative diseases, and (e) normal brain and adrenal CT scans. Manifestations of PAI included unprovoked: (a) hypotension, (b) hyponatremia, (c) hyperkalemia, and (d) progressive asthenia. Diagnosis of AD was confirmed with: low early morning basal serum cortisol (<185 nmol/L) and high plasma ACTH concentrations (>33 pmol/L) along with inadequate response to rapid ACTH stimulation test. In the latter test, a base line serum sample for cortisol was collected followed by another ones at time 30 minute and 60 minutes after an intravenous injection of 250 ug cosyntropin ($ACTH_{[1-24]}$). Inadequate response entails low peak concentration of serum cortisol (<500 nmol/L) [6].

2.2. Patients' Management

Initially, all suspected patients had received supportive care in the form of rapid infusion of isotonic saline followed by 5% glucose in isotonic saline and intravenous 4 - 6 mg of Dexamethasone. The triggering cause was dealt with. Subsequently tests were done to confirm disease. The latter included (a) serum levels of am serum cortisol and ACTH, (b) cosyntropin test, (c) laboratory and radiological tests to assess for infections and infiltrative diseases, (d) specific tests for autoimmune polyglandular syndrome type 1 and type 2, and (e) 21-hydroxylase antibodies by Enzyme-Linked Immunosorbent Assay (ELISA) [7].

2.3. Follow Up

Patients with confirmed disease had received Hydrocortisone 20 mg am with 10 mg pm and Fludrocortisone 50 - 100 mg daily. After their initial in-hospital stabilization, patients were assessed every 2 weeks for 6 weeks, every month for 3 months then every 2 months.

2.4. Statistical Analysis

SPSS statistical package version 26 was used for data entry and processing. Since age, creatinine clearance and am cortisol levels were normally distributed; they were expressed as means ± SD. On the other hand, duration of follow up was not normally distributed and hence was expressed as median(range).

3. Results

During the study period, a total of 22 patients were detected to have occult primary AD. However, only 19 patients were included. Exclusion of 3 patients, was due to: (a) death associated with severe sepsis (n: 1) and associated autoimmune or severe co-morbid conditions (n: 2) that prevented adequate testing and follow

up. The demographical data of the patients is summarized in Table 1. All patients were adults (53 ± 5 years) and 53% were females. Eleven (58%) patients had adequate kidney function while 6 (32%) were on maintenance hemodialysis and 2 (10%) on peritoneal one.

Table 1. Demographical data, presenting manifestations and unmasking events in renal patients with PAI.

Patients characteristics					
Total:	19				
Gender (F/M):	10/9				
Duration of follow up (months)*:	29 (2 - 60)				
AM serum cortisol**:	106 ± 22				
Multi-endocrine dysfunction:					
	Type 1	Type 2			
	2	5			
Autoantibodies to 21-hydroxylase:	16/19 (90%)				
At diagnosis:					
Age (years)**:	53 ± 5				
Stage of renal disease:					
	CRF	HD	PD		
	11	6	2		
Creatinine clearance**:	33 ± 5	<5	<5		
Presenting manifestation:					
	Hypotension	Cachexia	Hyponatremia	Hyperkalemia	Hypoglycemia
	11	2	2	2	2
Unmasking stress:					
	Sepsis	AKI	ACS	Psychosis	None
	5	4	3	1	6

Abbreviations: PAI: primary adrenal insufficiency, F: females, M: males, CRF: chronic renal failure. HD: hemodialysis, PD: peritoneal dialysis, AKI: acute kidney injury, ACS: acute coronary syndrome. *Expressed as median (range), **Expressed as means ± SD. Normal range of AM serum cortisol: 185 - 624 nmol/L.

3.1. Presenting Manifestations

As seen in Table 1, unprovoked hypotension was the most common manifestations of occult PAI and was the unmasking event in 11 (58%). It was without significant cardiac and/or severe systemic sepsis and was refractory to isotonic saline infusions. Equal number of the remaining patients (n = 2) presented with persistent and inexplicable electrolytes abnormalities viz. (a) hyponatremia despite restricted oral fluid intake, lack of dehydration and massive fluid overload, as well as (b) hyperkalemia despite potassium-restricted diet, hyperkalemic drugs

and adequate therapy with Furosemide and low-potassium dialysis-baths. On the other hand, similar proportions presented with unprovoked (c) progressive weight loss, decrease appetite and cachexia as well as (d) frequent hypoglycemic attacks.

3.2. Outcome

As seen in Table 1, 19 patients were medically stable after 29 (2 - 60) months of follow up.

3.3. Autoantibodies to 21-Hydroxylase Enzyme

A total of 16(90%) had positive antibodies.

3.4. Multi-Endocrine Dysfunction (MED)

At diagnosis, and subsequent follow up, only 7 patients (37%) had MED of whom 2 with type 1 and 5 with type 2.

4. Discussion

AD was named after Thomas Addison who first described it in his original monograph "the Constitutional and Local Effects of Disease of the Suprarenal Capsules" in 1855 [8]. Interestingly, all his 6 patients, had adrenal tuberculosis which was prevalent at that time [9]. In recent years, infiltrative diseases are early diagnosed and treated limiting the etiology of AD, in adults, to (a) Corticosteroid withdrawal and (b) autoimmune adrenalitis. The latter accounts for nearly 80% of cases of PAI and is characterized by the presence of: (a) antibodies to all 3 zones of the adrenal cortex, and (b) association with other autoimmune polyglandular dysfunction viz. type 1 (candidiasis, hypoparathyroidism, and primary gonadal failure) and type 2 is (primary hypothyroidism, primary hypogonadism, type 1 diabetes, and pernicious anemia). Adrenal autoantibodies are present in the serum of 60 to 75 percent of patients with primary adrenal insufficiency caused by autoimmune adrenalitis. In contrast, such autoantibodies are rarely found in patients with other causes of adrenal insufficiency, in first-degree relatives of patients with autoimmune primary adrenal insufficiency, or in normal subjects [10]. They are against the steroidogenic enzymes P450scc (CYP11A1, side-chain cleavage enzyme), P450c17 (CYP17, 17-alpha-hydroxylase), and P450c21 (CYP21A2, 21-hydroxylase) [11]. These enzymes are involved in the side-chain cleavage and subsequent hydroxylation of steroids. The autoantibodies to CYP21A2 are of the IgG1 or IgG2a subclass, suggesting that T helper (Th) cells are involved in destruction of the adrenal cortex in patients with autoimmune Addison disease [12]. In our study, the presence of adrenal autoantibodies in 90% of our patients confirmed the diagnosis of autoimmune adrenalitis. However, the association with MED was weak (37%) despite adequate duration of follow up (29 months). In our patients, PAI was occult and its manifestations were similar to those of CRF and its complications. High index of suspicion was

exerted to diagnose such disorder especially following acute adrenal crisis (AC) subsequent to multiple hypermetabolic triggers. AC is a life-threatening emergency and requires prompt therapeutic management including intravenous glucose and fluid resuscitation as well as stress dose hydrocortisone administration. Moreover, during times of stress viz. disease-states, sepsis, trauma and invasive surgical procedures, a higher stress-dose glucocorticoid is required to avoid AC. Management of primary adrenal insufficiency or autoimmune adrenalitis requires vigilance for concomitant autoimmune diseases; up to 50% of patients develop another autoimmune disorder during their lifetime [13].

5. Conclusion

To improve morbidity and mortality in patients with CRD vigilance for PAI should be exercised in those presenting with unprovoked malaise, weight loss, gastrointestinal disorders, hyperpigmentations, hypotension, hyponatremia, hyperkalemia, and hypoglycemia to avoid life-threatening AC.

Statement of Ethics

The case was reported according to World Medical Association Declaration of Helsinki.

There was no new or investigational drug added to the patient's maintenance therapy and they were not subjected to any harmful or injurious investigation.

Author's Contributions

Prof/Kamel El-Reshaid conceived of the study, participated in its design, and drafted the manuscript. Dr. Abdulmohsen Al-Bader participated in the study design, follow up of patients and data collection and tabulated the data. All authors read and approved the final manuscript.

Data Availability Statement

The data provided in the current review are available from the references.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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