ADDISON'S DISEASE : AN UNUSUAL CASE PRESENTATION

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Abstract

Addison's disease is a rare condition withan estimated incidence in the developed world of 0.8 cases per 100,000 and a prevalence of 4 to 11 cases per 100,000 population. Never the less, it is associated with significant morbidity and mortality, but once the diagnosis is made it can be easily treated. The symptoms vary in specificity from weakness, tiredness, fatigue, anorexia and gastrointestinal symptoms like nausea, vomiting, constipation, abdominal pain, and diarrhea to non-specific like salt craving, postural dizziness and muscle or joint pain. Biochemical abnormalities include hyponatremia and hyperkalemia. A definite diagnosis can be made by measuring ACTH and serum cortisol levels. We present a rare case of Addison's disease with Osteoarthritis in a 70 year old male who presented with a prolonged history of generalized joint pain with tenderness, stiffness and lack of flexibility along with nausea, vomiting, anorexia, weight loss and generalized hyperpigmentation of skin for 1 year. This is rather unique in the sense that the patients complained of the symptoms of Osteoarthritis several months prior to the diagnosis of Addison's disease and visited many specialists and primary health care providers only to be misdiagnosed. Therefore the purpose of this study is to outline the journey of this patient from the initial misdiagnosis to the eventual delayed diagnosis to the subsequent eventuality of death.

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Introduction

Addison's disease is a relatively uncommon disorder with a low prevalence in contrast to other endocrine abnormalities like diabetes and thyroid disease. Never the less, it is associated with significant morbidity and mortality, but once the diagnosis is made itcan be easily treated[1]. However, it is often difficult to diagnose due to its varied presentation and so remains mostly undetected in the early part of its presentation. This is a problem especially in developing countries where there is lack of appropriate facilities for special investigations and a general unawareness amongst clinicians who are not so familiar with the disease[2]. Worldwide, infectious diseases are the most common cause of primary adrenal insufficiency. These diseases include tuberculosis, fungal infections (Histoplasmosis,Cryptococcus's) and cytomegalo virus[3]. In the Western world, autoimmune adrenalitis accounts for more than 70% of all cases of primary hypoadrenalism[3,4].

Patients with primary adrenal failure usually have both glucocorticoid and mineralocorticoid deficiency.The clinical features relate to the rate of onset and the severity of adrenal deficiency[1]. Alternatively, the patient may present with vague featuresof chronic adrenal insufficiency like weakness, tiredness,weight loss, nausea, intermittent vomiting, abdominalpain, diarrhea or constipation, general malaise, musclecramps, arthralgia, and symptoms suggestive of postural hypotension (Table I). The most obvious feature that differentiates primary from secondary hypoadrenalismis skin pigmentation which isalmost always present in cases of primary adrenal insufficiency (Unless of short duration) and absent in secondary insufficiency. The pigmentation is seen in sun-exposedareas, recent rather than old scars, axillae, nipples, palmarcreases, pressure points, and mucous membranes (Buccal,vaginal, vulval, anal).Salt craving may be a feature, and a low-grade fever may be present[5]. Supine blood pressure is usually normal, but almost invariably there is a fall in blood pressure on standing. There are several uncommon presentation of the disease and very few studies have examined the correlation[6].

Table I : Clinical Features of Primary Adrenal Insufficiency

Clinical Features of Primary Adrenal Insufficiency

Feature	Frequency (%)
Symptoms	
Weakness, tiredness, fatigue	100
Anorexia	100
Gastrointestinal symptoms	92
Nausea	86
Vomiting	75
Constipation	33
Abdominal pain	31
Diarrhea	16
Salt craving	16
Postural dizziness	12
Muscle or joint pains	13
Signs	
Weight loss	100
Hyperpigmentation	94
Hypotension (<110 mm Hg systolic)	88-94
Vitillgo	10-20
Auricular calcification	5
Laboratory Findings	
Electrolyte disturbances	92
Hyponatremia	88
Hyperkalemia	64
Hypercalcemia	6
Azotemia	55
Anemia	40
Eosinophilla	17

Case Report

A 70 year old male came to our Out-Patient Department with complaints of generalized joint pain with tenderness, stiffness and lack of flexibility along with nausea, vomiting, anorexia, weight loss and generalized hyperpigmentation of skin for 1 year. He visited many physicians of various specialties ranging from Gastroenterologists, Internists, Rheumatologists and General Practioners (GPs) with these vague symptoms and complaints but they could not diagnose him appropriately because of his atypical presentation. He was diagnosed as a case of Psoriatic Arthritis by an Internist and was given Methotrexate and Sulfasalazine with which his symptoms did not improve. Moreover, after several weeks he suddenly developed persistent vomiting resulting in unconsciousness and was thereby admitted in an Intensive Care Unit (CU) of a local hospital. After 2-3 days his symptoms improved and he was discharged. However, the patient could not give a proper history of his appropriate treatment in the ICU and further more he felt better and was symptom free for the next couple of weeks until his symptoms of vomiting, nausea and weakness remitted and this time he decided to consult an Endocrinologist with the advice of his Primary Care Physician. The Endocrinologist made a preliminary diagnosis of Addison's disease based on the clinical presentation of blackening of oral mucosa, Hard palate and palmar crease, recurrent hypoglycemic episodes and Orthostatic Hypotension (BP 80/60 in standing position as opposed to 110/80 in lying position). He was clinically dehydrated and tachycardic.

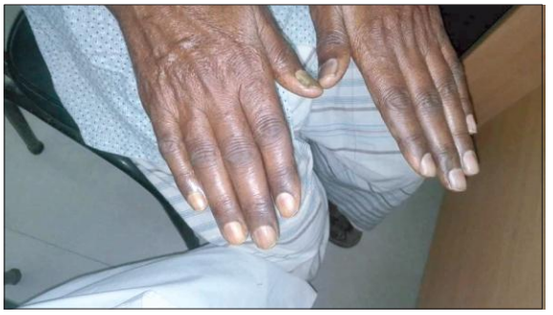

Figure 1 : Generelized hyperpigmentation of the palmar creases

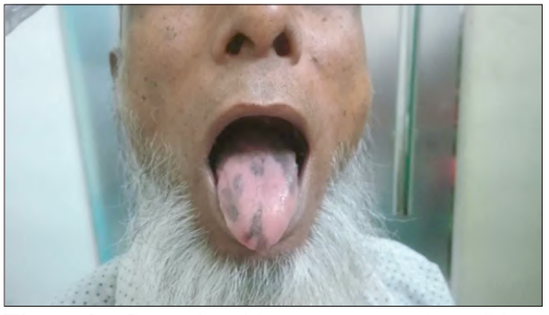

Figure 2 : Generelized hyperpigmentation of the tongue

Investigations

The patient was hyponatraemic with Serum Sodium levels of 123.60 mmol/l (Normal 135-148 mmol/l) potassium levels normal at 4.54 mmol/l (Normal 3.5–5.3 mmol/l) liver and kidney function tests were normal, Serum TSH was 2.05 µIU/ml (Normal 0.350-5.00 µIU/ml) Random Blood Sugar (RBS) was 8.22 mmol/l (Normal up to 7.8 mmol/l) and HbA1C of 5.7% (Normal 4.2-6.2%). CBC levels demonstrated a slight eosinophilia, elevated WBC counts with haemoglobin levels of 15.5 g/dl (14-18 g/dl). Serum Protein

Electrophoresis was suggestive of acute infection/inflammation. Urine R/E and Chest X-Ray were found unremarkable. An USG of Whole Abdomen revealed Cholelithiasis and Grade II Fatty liver and an Endoscopy of Upper GIT revealed Antral Gastritis. Serum Uric Acid and Fasting Lipid Profiles were well within the reference ranges. C - Reactive Protein (CRP) Rheumatoid Factor (RF) Anti-Nuclear antibody (ANA) and Anti-CCP antibody were negative. An X-ray Pelvis revealed reduced bone mineralization and normal joint spaces. CT-Scan of Brain was found normal. His diagnosis was confirmed significantly reduced early morning cortisol levels of 0.3 µg/dl (Normal 4.82-19.5 µg/dl) and significantly elevated ACTH levels of >1500 pg/ml (Normal 5.00 – 46.00 pg/ml).

Treatment

After confirming his diagnosis the patient was prescribed on oral prednisolone (10 mg at morning and 5 mg at afternoon) and fludrocortisone (50-100 micrograms OD) at the recommended physiological maintenance doses along with plenty of fluid intake and educated about the importance of compliance.

Outcome and Follow-up

The patient was discharged home with the aforementioned treatment with a condition to follow-up after one month. Unfortunately he was very irregular as he resided in a remote location and in spite of showing some early improvement of signs and symptoms he finally succumbed to the disease after 3 months after a recurrent bout of diarrhea and fever with features of adrenal crisis due to poor compliance.

Discussion

Addison's disease is a rare condition withan estimated incidence in the developed world of 0.8 casesper 100,000 and a prevalence of 4 to 11 cases per 100,000 population. Never the less, it is associated with significant morbidity and mortality, but once the diagnosis is made it can be easily treated[1, 7]. There is currently no data on the incidence and prevalence of Addison's disease in Bangladesh. There is a significant delay in diagnosis because of the vague signs and symptoms and varied presentation of the disease and lack of specialist centers. The symptoms vary in specificity from weakness, tiredness, fatigue, anorexia and gastrointestinal symptoms like nausea, vomiting, constipation, abdominal pain, and diarrhea to nonspecific like salt craving, postural dizziness and muscle or joint pain[8, 9].

Routine biochemical profiles include hyponatremia (90%) hyperkalemia (65%)[8,9]. Reversible abnormalities in liver transaminases frequently occur. Hypercalcemia occurs in 6% of all cases and may be particularly marked in patients with co-existingthyrotoxicosis[10]. Free thyroxine concentrations are usually low or normal, but TSH values are frequently moderately elevated[11]. Clinical suspicion of the diagnosis should be confirmed with definitive diagnostic tests. Basal plasma cortisol andurinary free cortisol levels are often in the low-normal range and can not be used to exclude the diagnosis. Inpractice, rather than wait for results of insensitive basal tests, all patients with suspected adrenal insufficiency should have an ACTH stimulation test, in patients with an Addisonian crisis, however, treatment should be instigated immediately and stimulation tests conducted at a later stage[8]. Radioimmunoassay's to detect auto antibodies such as those against the 21-hydroxylase antigen are now available and should be analyzed in patients with primary adrenal failure. In autoimmune Addison's disease, it is also important to look for evidence of other organ-specific autoimmune disease. A CT scan of abdomen may reveal enlarged or calcified adrenals, suggesting an infective, hemorrhagic, or malignant diagnosis. Chest radiography, tuberculin testing, and early-morning urine samples cultured for Mycobacterium tuberculosis should be performed if tuberculosisis suspected. CT-guided adrenal biopsy may reveal an underlying diagnosis in patients with suspected malignant deposits in the adrenal[8].
Acute adrenal insufficiency is a life-threatening emergency and treatment should not be delayed while waiting for definitive proof of diagnosis. However, inaddition to measurement of plasma electrolytes and blood glucose, appropriate samples for ACTH and cortisol should be taken before corticosteroid therapy is given. If the patient is not critically ill, an acute ACTH stimulation test can be performed. In adults, intravenous hydrocortisone should be given in a dose of 100 mg every 6 to 8 hours. If this is not possible,then the intramuscular route should be used. In the patient with shock, 1 L of normal saline should be given intravenously over the first hour. Because of possible hypoglycemia, it is normal to give 5% dextrose in saline. Subsequent saline and dextrose therapy will depend on biochemical monitoring and the patient's condition. Clinical improvement, especially in the blood pressure, should be seen within

4 to 6 hours if the diagnosis is correct. It is important to recognize and treat any associated condition (e.g infection) that may have precipitated the acute adrenal crisis. After the first 24 hours, the dose of hydrocortisone can be reduced, usually to 50 mg intramuscularly every 6 hours and then to oral hydrocortisone, 40 mg in the morning and 20 mg at 6 p.m.. This can then be rapidly reduced to a more standard replacement dose of 20 mg on wakening and 10 mg at 6 p.m[8].

The aim of long-term therapy is to give replacement doses of hydrocortisone to mimic the normal cortisol secretion rate. In primary adrenal failure, mineralocorticoid replacement is usually also required in the form of fludrocortisone (or 9 -fluorinated hydrocortisone) 0.05 to 0.2 mg/day. After the acute phase has passed, the adequacy of mineralocorticoid replacement should be assessed by measuring electrolytes, supine and erect blood pressures, and plasma renin activity[12]. Too little fludrocortisone may cause postural hypotension with elevated plasma renin activity, whereas too much causes the converse.Mineralocorticoid replacement therapy is all too frequently neglected in patients with adrenal failure.

This case presented with complaints of generalized joint pain with tenderness, stiffness and lack of flexibility, features of Osteoarthritis long before the more prominent signs of generalized hyperpigmentation of skin and hypotension which prompted the physicians towards a misdiagnosis, subsequently a delayed diagnosis and hence a delay in treatment. This rare presentation of Osteoarthritis prior to the presentation of Addison's disease is rather unusual and it is only when the symptoms of osteoarthritis had attenuated that the physician was prompted to undergo the various investigations leading to the proper diagnosis.

It has been suggested that other factors are also likely to be associated with bone loss in these patients and that an intrinsic risk of bone loss in autoimmune hypoadrenalism can not be ruled out. Recent evidence also found significant rates of osteoarthritis among autoimmune hypoadrenalism patients. 13% of patients with autoimmune adrenal failure reported osteoporosis or osteopenia and a further 12% reported osteoarthritis[6]. Furthermore, other researchers have also identified an intrinsic risk of bone loss for diabetes, rheumatoid arthritis and asthma in patients with primary adrenal insufficiency[13-15].

Conclusion

Therefore the unusual presentation and clinical course of the disease suggests that the proper diagnosis can be confirmed by careful scrutiny and appropriate history taking early on the onset of the disease with the specific investigations which could prompt the investigator to reach an affirmative diagnosis and save the life of the patient through education and counseling with adequate medications and assured follow-up.

Contribution of Authors-Equal

Disclosure

All the authors declared no competing interests.

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