Case Report

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Internal Medicine Section

Delayed Diagnosis of Graves' Thyrotoxicoisis Presenting as Recurrent Adrenal Crisis in Primary Adrenal Insufficiency

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ABSTRACT

Adrenal crisis is a potential life threatening complication. The common causes of adrenal crisis are infections, surgical stress and abrupt cessation of steroid medications. Endocrine causes like Graves' disease with thyrotoxicosis is one of the less common causes of an adrenal crisis. We report a 42-year-old female who presented with recurrent episodes of adrenal crisis due to delayed diagnosis of thyrotoxicosis. She was initially treated with Carbimazole followed by Radio-iodine ablation and currently she is euthyroid. Her adrenal insufficiency was initially treated with hydrocortisone during the time of adrenal crisis followed by Prednisolone 5 mg once daily in the morning along with fludrocortisone 50 mcg once daily. This case highlights the need for high index of suspicion and less common causes like thyrotoxicosis should be ruled out in patients with adrenal crisis.

Keywords: Graves' disease, Hydrocortisone, Prednisolone

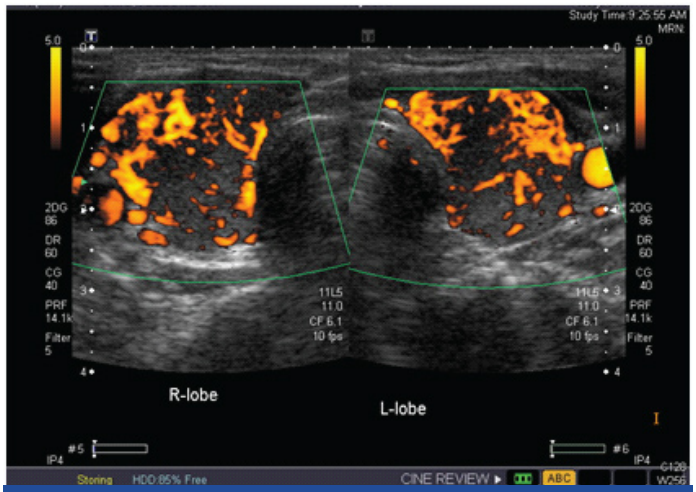
CASE REPORT

A 42-year-old female diagnosed with primary adrenal insufficiency, 2 years prior in another institution, was referred to the department of Endocrinology for the persistence of tiredness, weakness, giddiness and progressive weight loss. She was being previously evaluated for symptoms of vomiting, abdominal pain and refractory hypotension. Her blood investigations then had showed a random serum cortisol of 2 µg/dl dl, (Normal 5-27µg/dl), serum sodium of 123 mEq/L(135-145), potassium of 5.6mEq/L (3.5-5) and plasma ACTH of 345 pg/ml (0-45),all were suggestive of primary adrenal insufficiency. Her Chest X ray, CT abdomen with contrast and thyroid function were all within normal limits during the time of initial admission. Thus final diagnosis of primary adrenal insufficiency with adrenal crisis was considered and was initially treated with intravenous hydrocortisone followed by twice daily dose of 5mg oral prednisolone. She was apparently asymptomatic for 1 and ½ years from the time of her initial diagnosis of primary adrenal insufficiency. Six months prior to an episode of of an adrenal crisis the patient noticed symptoms of fatigue, weakness, weight loss, giddiness and increasing hyper pigmentation. She was admitted twice to hospital with features suggestive of adrenal crisis requiring intravenous hydrocortisone and Intravenous fluids for improvement. The time interval between the first and second episode of adrenal crisis was 4 months. ACTH or CRH stimulation tests were not done during the follow-ups. During both these episodes of adrenal crisis she had no other precipitating factors such as fever, diarrhea or any infection.

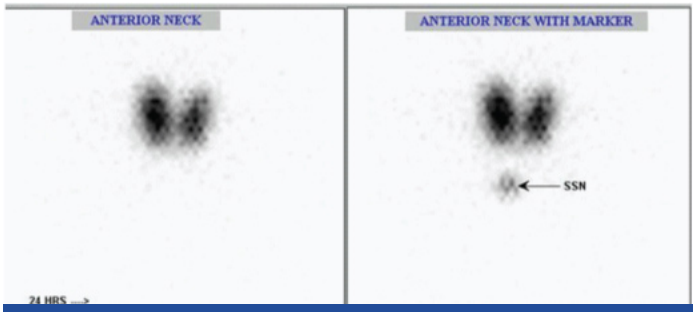
The diagnosis of adrenal crisis was considered based on the clinical features (vomiting, abdominal pain hypotension, weight loss) in the setting of underlying primary adrenal insufficiency. Details of previous biochemical investigations (sodium, potassium, plasma glucose or arterial blood gas analysis) reports during the admission for adrenal crisis were not available with the patient and hence could not be evaluated.

Due to recurrent episodes of crisis the dose of prednisolone was increased to 10mg in the morning and 5mg in the evening. Even then she continued to have persistence of symptoms with progressive weight loss, for which she was referred for further evaluation. However, she was not evaluated for malabsoption or any gastro intestinal related other disorders to rule out possibility of poor intestinal absorption of prednisolone. On the other hand she did not have symptoms of alerted bowel habits (on and off diarrhea or constipation).

During evaluation at the time of present admission, she was a thin build lady with hyper-pigmentation of the oral mucosa, palmar creases of both hands and extensor aspects of both arms with no vitiligo. Her supine neck examination showed a WHO grade –II diffuse thyromegaly and there were no obvious signs of thyrotoxicosis (fine tremor, prominence of eye balls) and there was no thyroid bruit. Her supine blood pressure was 100/70 mmHg and on standing, the blood pressure was 90/60 mmHg and pulse was 120/minute. In view of her symptoms suggestive of adrenal crisis, she was immediately started on injectable hydrocortisone on an outpatient basis. She was post menopausal by three years. At the time of admission to our hospital her random serum cortisol was of 0.71µg/dl (normal 5-27µg/dl) and plasma ACTH of 560 pg/ml (Normal 0-46pg/ml). The investigations for thyroid status showed TSH –0.004µIU/ml (normal: 0.3-4.5), T4 –30 µg% (8-12), and FT4 –6.82 ng% (0.8-1.8) which was suggestive of thyrotoxicosis. Her thyroid receptor antibody (TSI) level was 8.1 µ/L (Normal 1-5), anti-peroxidase autoantibody (anti –TPO) was 514 IU/ml (<50) by ELISA. Her ultrasound of thyroid showed a



[Table/Fig-1]: USG doppler image showing an increased internal vascularity in both lobes of the thyroid.



[Table/Fig-2]: I^{131} thyroid uptake scans showing an increased radiotracer uptake even after 24 hours.

diffuse enlargement of both lobes with an increased vascularity [Table/Fig-1] and radioiodine uptake study showed increased radioiodine uptake at 1 hours - 70%; 6 hours-92% and 24 hours -90% with diffuse uptake of both lobes [Table/Fig-2] suggestive of Graves' thyrotoxicosis. Other investigations revealed FSH of 71.1mIU/ml, electrolyte sodium of 136 mEq/L, potassium 4.0 mEq/L, creatinine of 0.45 mg% (normal 0.5- 1.4) and Vitamin B12 of 340.6 pg/ml (normal 200-950) .

She was initially started on carbimazole 30 mg once daily for 2 months period to achieve a biochemical control. Along with the antithyroid medication, she was started with tablet prednisolone 7.5 mg in the morning and 2.5 mg in the evening and fludrocortisone 50 mcg once daily. On follow up after 2 months, she was symptomatically better and her thyroid function showed T4 of 15.7 µg% and FT4 of 2.35 ng/ µg%. Subsequently she was treated with 5 millicurie radio-iodine (I-131), and following which her anti-thyroid drug was discontinued. She is currently on regular follow up with oral prednisolone 5mg in the morning along with fludrocortisone 50 mcg once daily dose. Her recent thyroid function was suggestive of euthyroid status (TSH – 2 µIU/ml T4 – 8.2 µg% and FT4 of 0.93 ng %), thus not requiring any treatment for her thyroid disorders. She is presently asymptomatic and has gained 8 kilograms over a period of one year. She has been educated regarding the corticosteroid dose adjustment during the stressful condition such as fever, vomiting and diarrhea and was also educated for hydrocortisone self injection.

DISCUSSION:

Adrenal insufficiency

Adrenal insufficiency is a disorder characterized by failure of production of hormones from adrenal cortex. Adrenal insuffiecncy are of two types, primary and secondary adrenal insufficiency. In primary adrenal insufficiency disease is confined to the adrenal while in secondary adrenal insufficiency occurs either due to suppression from chronic steroid hypothalamic-pituitary adrenal axis or hypopituitarism due to hypothalamic – pituitary disease [1]. The diagnosis of primary adrenal insufficiency is always based on clinical presentation, low serum cortisol level and high ACTH level. The ACTH (synacthen) stimulation is of great value in patients with adrenal insufficiency. The Synacthen stimulation test can be performed immediately in hemodynamically stable patients or can perform during follow up after clinical improvement to establish the diagnosis of adrenal insufficiency. A Serum cortisol level of ≤18µg/dl, 60 minutes after 250 mcg of intravenous synacthen is suggestive of adrenal insufficiency [2]. However in the clinical setting of primary adrenal insufficiency dynamic testing is not essential when, serum cortisol levels is <3 µg/dl with considerable elevated ACTH (100 pg/ml) [3].

Adrenal Crisis (AC) is a life threatening complication seen in both primary and secondary adrenal insufficiency. It requires immediate diagnosis and treatment to avoid potential mortality due to a crisis. The overall frequency of AC varies from 3.3 -6.3% per 100 patients per year. According to UK - Addison's Disease Self-Help Group data 47% of patients with chronic adrenal insufficiency had at least one admission in the emergency department or hospitalization for adrenal crisis, in about 10.6% of patients with primary adrenal insufficiency and 7.47% with secondary adrenal insufficiency had four or more episodes of hospitalization [4,5]. The diagnosis of adrenal crisis is always presumptive and primarily based on clinical presentation (vomiting, abdominal pain and fatigue), physical examination (dehydration, hypotension) in the setting of underlying adrenal insufficiency. The typical biochemical features of adrenal crisis are hyponatraemia, hyperkalaemia and hypoglycaemia. Treatment of adrenal crisis must not be delayed for diagnostic investigations or biochemical reports.

Adrenal crisis can be the first presenting symptom in patients with acute adrenal insufficiency and it is by and large due to delay in the diagnosis. In chronic adrenal insufficiency, AC can be triggered by various systemic causes such as vomiting, diarrhea, infection, accident, surgery, myocardial infarction, psychiatric disorders, pregnancy, extreme climatic change, severe migraine, long distant flight, epilepsy and abrupt cessation of medications. The other causes of adrenal crisis include drugs which inhibit endogenous cortisol synthesis (etomidate, ketoconazole) or which increases rate of cortisol metabolism (rifampicin, sorafenib, mitotane and barbiturates). Malabsorption related disorders such as celiac disease, atrophic gastritis, cystic fibrosis, pancreatic insufficiency or drug induced (laxative) can precipitate an adrenal crisis by affecting therapeutic hydrocortisone profile [6]. There are certain endocrine causes that can precipitate AC in adrenal insufficiency like initiation of levothyroxine in patients with undiagnosed adrenal insufficiency, new onset of thyrotoxicosis in the setting of chronic adrenal insufficiency and following bilateral adrenalectomy for Cushing's disease [7].

Primary adrenal insufficiency can be associated with thyroid disorders such as autoimmune thyroiditis and hypothyroidism as a part of the Schmidt syndrome. In children with type -1 diabetes with adrenal insufficiency, hypothyroidism usually suspected when patients had increase frequency of hypoglycaemia.

The association between hyperthyroidism and primary adrenal insufficiency is found to be rare. The incidence of thyrotoxicosis in patients with Addison's disease in about 5% which is nearly 10 times when compared to the general population [8]. There are a few case reports of thyrotoxicosis not being recognized initially in patients with primary adrenal insufficiency when both clinical conditions present simultaneously or vice versa [9,10]. The clinical features of both diseases are almost similar and sometimes coexisting features are wrongly attributed to dominant disease and diagnosis often delayed. Such patients are more susceptible to adrenal crisis [11]. There are several case reports of thyrotoxicosis precipitating adrenal crisis in patients with chronic adrenal insufficiency. Nagai et al., reported a case of lithium induced transient thyrotoxicosis precipitated adrenal crisis in a patient with unilateral adrenalectomy for adrenal Cushing's syndrome. She was previously treated with lithium for manic depressive illness due to Cushing's syndrome [12]. Onuk et al., reported a case of adrenal crisis in a patient with type 2 diabetes with CAD following treatment with amiodarone for post CABG atrial fibrillation. Yoshino et al., reported similar case of sunitib induced thyrotoxcosis precipitating adrenal crisis in a patient with renal cell carcinoma [13]. Shaikh et al., reported case of adrenal crisis following thyroxine in patients with undiagnosed primary adrenal insufficiency. Lewandowski et al., reported a case of Graves' thyrotoxicosis precipitating adrenal crisis in a patient with panhypopituitarism [14].

The mechanism of adrenal crisis in the setting of thyrotoxicosis is mainly related to increased rate of cortisol metabolism due to increased hepatic 4, 5-reductase activity. In thyrotoxicosis, the adrenal cortical function is affected due to an increased rate of clearance and increased rate of production of cortisol, however

the circulating cortisol levels remain normal [15]. There are studies showing diminished adrenal reserve in subjects with prolonged severe thyrotoxicosis and normalization of cortisol levels following treatment of thyrotoxicosis. In the setting of a thyroid storm, the normal cortisol level is often interpreted as relative adrenal insufficiency. Our case in many ways differs from other causes of adrenal crisis as thyrotoxicosis is not a common cause of adrenal crisis in primary adrenal insuffiecncy. On other hand in our patient the clinical features of thyrotoxicosis were subclinical. This case highlights the need for a high index of suspicion and rare cause like thyrotoxocosis should be rule to in patients with adrenal crisis. Thyroticosis should also be suspected when there recurrent episode of adrenal crisis This case also highlights the need for routine performing of thyroid function even in patients presenting with adrenal crisis to rule out thyrotoxicosis, rather than looking for hypothyroidism alone.

CONCLUSION

It is imperative for the physician to suspect Graves' thyrotoxicosis as one the important cause of the adrenalcrisis when patients fail to improve symptomatically or have recurrent episodes of adrenal crisis even with adequate steroid replacement after the common causes like infection and stress had been excluded. Even though the association of Addison's disease and Graves' thyroxicosis is uncommon, it requires a high index of suspicion for early diagnosis and treatment to prevent death due to adrenal crisis. It is also essential onthe part of the doctor to ensure that the patient carries the emergency medicines and to also educate the patient regarding the need of glucocorticoids dose adjustment during illness and injury.

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