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Adrenal Crisis with Hypercalcemia Precipitated by Levothyroxine Initiation in a Patient with Polyendocrinopathy

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Abstract

Polyglandular autoimmune syndrome type 2 involving autoimmune primary adrenal insufficiency and autoimmune hypothyroidism is rare. Fatigue and tiredness are common overlapping symptoms between the two conditions. Initiating levothyroxine in a patient with underlying adrenal insufficiency may precipitate a severe adrenal crisis. Here, we report a case of a 21-year-old lady who presented with an adrenal crisis with hypercalcemia after levothyroxine initiation. This case highlights the importance of taking a proper detailed history and diligent physical examination which can direct the appropriate diagnosis and avoid the preventable consequence.

Keywords

- Addison disease
- adrenal crisis
- hypercalcemia
- hypothyroidism
- polyendocrinopathy syndromes

Introduction

Polyglandular autoimmune syndrome type 2 (PAS-2) is an autoimmune syndrome that is diagnosed with two out of three of the following: autoimmune primary adrenal insufficiency (PAI), autoimmune thyroid disease-causing Grave's disease or hypothyroidism, and type 1 diabetes mellitus (T1DM).[1] APS-2 has a prevalence of 1 in 100,000 and it occurs more commonly in women with a ratio of at least 3:1 compared with men with a peak incidence between age 20 and 60 years of age.[2] The patient may present with isolated endocrine organ dysfunction and other endocrine and non-endocrine associations may develop later. Therefore, the diagnosis of PAS-2 is often delayed. It has been shown that autoimmune thyroid disease and T1DM are the most prevalent endocrine dysfunctions in patients with PAS-2 constituting 65.6 and 60.9%, respectively. Addison's disease was found in 18.5% of the patients. Therefore, the coexistence of thyroid disease and T1DM was most common while a combination of Addison and thyroid diseases was less frequent.[3] However, adrenal insufficiency can be the initial manifestation in about half of the cases, and patients with Addison disease in PAS-2 have a 2.5-fold increased risk of adrenal crisis.[4,5] Initiation of levothyroxine in patients with untreated PAI may precipitate an adrenal crisis. Furthermore, hypercalcemia is infrequent or underrecognized in adrenal insufficiency with a prevalence of approximately 6.5 to 8.4%.[6]

In this case report, we present a young lady who developed an adrenal crisis and hypercalcemia after levothyroxine initiation.

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Case Presentation

A 21-year-old female presented to the emergency department with a 2-day history of recurrent episodes of nausea and vomiting associated with extreme fatigue, tiredness, and body aches. Six months back, she gave birth to a healthy baby girl through normal vaginal delivery in another health care facility. During her pregnancy, she complained of consistent fatigue, tiredness, intermittent dizziness, and poor appetite that persisted postdelivery. Furthermore, she reported a weight loss of 12 kg over 12 months' period. In addition, she noticed generalized skin darkness and focal hyperpigmentation in certain parts of her body. Four weeks before the current presentation, she was diagnosed with primary hypothyroidism for which levothyroxine 75 mcg was initiated (no details of baseline thyroid function test [TFT] available). Her family history was remarkable for T2DM in both parents.

On physical examination, she was alert and oriented but clinically dehydrated and sick-looking. Her vitals showed lying blood pressure of 84/53 mm Hg, pulse rate of 117 beats per minute, respiratory rate of 18 breaths per minute, temperature of 36.7°C, and oxygen saturation of 98% on room air. Apart from sunken eyes, cracked lips, and poor skin elasticity, skin examination showed generalized darkness and patchy hyperpigmentation of the lips, tongue, buccal mucosa, palm creases, and knuckles areas. No vitiligo or alopecia. Thyroid examination revealed mild smooth nontender diffuse thyromegaly. The rest of the systemic examination was unremarkable.

Initial laboratory findings (►**Table 1**) revealed hypovolemic hypotonic hyponatremia of 128 (136–145) mmol/L, hyperkalemia 6.0 (3.2–5.5) mmol/L, acute kidney injury stage 1 with creatinine levels of 106 (44–80) mmol/L, and urea 8.14 (2.8–8.10) mmol/L. In addition, corrected calcium level was elevated of 3.21 (2.10–2.60) mmol/L along with low parathyroid hormone (PTH) levels of 0.3 (1.6–6.9) pmol/ L. Venous blood gas showed a normal anion gap metabolic acidosis with a low pH of 7.24 (7.35–7.45), low bicarbonate of 18 (22–26) mmol/L, and lactic acid 1 (0.5–2.2).

Initially, she was resuscitated with 2 L intravenous normal saline 0.9% bolus followed by continuous infusion. As an adrenal crisis was suspected, an intravenous 100 mg hydrocortisone bolus dose was administered followed by a maintenance dose of intravenous hydrocortisone 50 mg every 6 hours. Additionally, she received antihyperkalemia measures with nebulization, insulin, and calcium polystyrene. Initially, antibiotics (amoxicillin-clavulanic acid 1 g every 8 hours) were started to cover any possible infection, which was discontinued later as no infection source was identified. Her blood pressure improved to 100/50 mm Hg and her potassium level decreased to 5.2 mmol/L.

Subsequent laboratory findings (►**Table 1**) revealed low random cortisol 17 (64–536) nmol/L (sample taken before hydrocortisone administration), relatively low aldosterone of 29.67 (28.8–158) pg/mL with elevated adrenocorticotropic hormone 430 (1.6–13.9) pmol/L and renin 100 (4–23.7) ng/L, and positive 21 hydroxylase antibodies consistent with autoimmune PAI (Addison disease). TFT showed elevated thyroid-stimulating hormone (TSH) 21.5 (0.4–4.2) mIU/L and low free T4 11.2 (12–22) pmol/L with positive thyroid antibodies suggestive of Hashimoto's related hypothyroidism. Complete blood count showed microcytic hypochromic anemia of 10.4 (117–155) g/L. The iron profile showed a low ferritin 5 (5.8–34.5) mcmol/ L. Celiac profile with anti-gliadin I and antitissue transglutaminase immunoglobulin A antibodies were negative. B12 level was not performed.

During admission, the patient improved gradually, clinically and biochemically. She was able to take orally and move around without nausea, vomiting, or dizziness. Laboratory investigation before discharge revealed normal creatinine, urea, and corrected calcium levels of 75, 6.7, and 2.36 mmol/L, respectively. On day 5 of admission, she was discharged on oral hydrocortisone (25 mg total daily dose) along with fludrocortisone 0.1 mg daily and levothyroxine 25 mcg daily.

Discussion

In this report, we present a case that illustrates two important aspects of the adrenal crisis in the same patient. First, the initiation of levothyroxine in patients with adrenal insufficiency may manifest the disease and even precipitate an adrenal crisis.[4,7] In our reported case, the patient had longstanding symptoms and signs of PAI that could be detected through a detailed history and physical exam and if done would avoid a precipitating adrenal crisis with levothyroxine initiation.

There have been multiple explanations for the underlying pathophysiology including that the hypothyroid state is a catabolic state requiring low cortisol levels. Supplementation with levothyroxine increases the metabolic rate and anabolic state and therefore increases the demand for cortisol in patients with already limited production reserve. In addition, thyroid hormone plays a role in cortisol clearance and levothyroxine initiation enhances hepatic glucocorticoid metabolism, decreasing the availability of already low cortisol.[4]

It is worth mentioning that elevated TSH is frequently recorded in almost half of patients with Addison's disease.[8] The high TSH value could indicate untreated hypothyroidism but might also be a sign of unrecognized adrenal insufficiency due to the loss of inhibitory effect of cortisol on pituitary TSH production.[9] Since we did not have access to the patient's first TFT, we are not sure whether she had true hypothyroidism or TSH elevation secondary to the loss of the inhibitory effect of cortisol. However, she does have positive thyroid autoantibodies.

Therefore, in patients with persistent elevation in TSH despite levothyroxine escalation along with worsening symptoms of fatigue and dizziness, it is worth expanding the differential diagnosis and considering the possibility of adrenal insufficiency. Electrolyte imbalance with hyponatremia and hyperkalemia may support this differential

Table 1 Laboratory results

Laboratory parameter	Patient value	Reference range
Urea and electrolytes		
Sodium (mmol/L)	128	135–145
Potassium (mmol/ L)	6	3.2–5.5
Creatinine (mmol/L)	106	44–80
Urea (mmol/L)	8.14	2.80–8.10
HCO3 (mmol/L)	18	22–32
Complete blood count		
Hgb (g/L)	104	117–155
Hct (L/L)	0.31	0.35–0.45
MCV (fL)	75.1	81–100
White blood cell count (*10^9/L)	8.6	4.5–11
Platelets (*10^9/L)	347	140–400
Biochemistry		
C-reactive protein (mg)	70.5	< 5
TSH (mIU/L)	21.5	0.4–4.2
T4 (pmol/L)	11.2	12–22
Random cortisol (nmol/L)	17	64–536
ACTH (pmol/L)	430	1.6–13.9
Aldosterone (pg/mL)	29.67	28.8- 158
Renin (ng/L)	100	4–23.7
Corrected calcium (mmol/L)	3.21	2.10–2.60
Phosphate (mmol/L)	0.93	0.81–1.45
Intact PTH (pmol/L)	0.3	1.6–6.9
Autoimmune antibodies		
TPO (IU/mL)	86	< 34
Thyroglobulin (IU/mL)	590	< 115
21 hydroxylase antibodies	Positive	Negative

Abbreviations: ACTH, adrenocorticotropic hormone; Hct, hematocrit; Hgb, hemoglobin; MCV, mean corpuscular volume; PTH, parathyroid hormone; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

where it has been reported in 84 and 34%, respectively, in patients with Addison disease.[8]

The second point is hypercalcemia in adrenal insufficiency which is a rare cause of PTH-independent hypercalcemia as mentioned earlier. It has been reported in both primary and secondary adrenal insufficiency with different etiologies like histoplasmosis,[9] opioid-induced adrenal insufficiency,[10] lymphocytic hypophysitis,[11] and glucocorticoid-induced adrenal insufficiency.[12] More recently, it has been reported secondary to hypophysitis related to immunotherapy.[13] It has been hypothesized that the hypercalcemia mechanism in adrenal insufficiency is multifactorial though it remains unknown. Mineralocorticoid deficiency induces hypovolemia leading to decreased glomerular filtration rate and calcium filtration at the glomerulus; therefore, calcium and sodium reabsorption increase at the proximal tubule. Hydration with intravenous fluid therapy corrects volume depletion and calcium levels by enhancing its clearance. Another mechanism is the increased activity of renal 1-α- hydroxylase enzyme converting 25(OH)-vitamin D to its active form 1,25(OH)-vitamin D. Intestinal and renal absorption of calcium increases due to increased active vitamin D levels.[14] We did not measure the PTH-related protein level and 1,25(OH)2D level in this patient as it was deemed unnecessary and unavailable in-house.

Managing hypercalcemia in adrenal insufficiency involves not only lowering calcium levels but mainly replacing glucocorticoids. As mentioned earlier, hydrating with intravenous fluids would lower calcium levels by increasing the glomerular filtration rate and its clearance as sodium gets reabsorbed in exchange for calcium at the proximal tubules. Loop diuretics are not recommended as they decrease volume and cause further electrolyte derangements. Administering glucocorticoids is the cornerstone to normalize calcium levels. As it takes time for glucocorticoids to be replaced efficiently, other medications can be used temporarily such as calcitonin and bisphosphonates if needed. Calcitonin is a polypeptide synthetic hormone that increases calcium excretion. Intravenous bisphosphonates are contraindicated in kidney injury as there is a risk of acute tubular necrosis and glomerular sclerosis. Finally, hemodialysis can be considered as a last measure in cases of either refractory hypercalcemia or advanced oliguric renal failure. It is considered to be the most effective method to lower severe hypercalcemia rapidly.[15]

Conclusion

This case highlights important lessons including the importance of detailed history and physical examination that may direct toward possible PAI and avoid the consequence of adrenal crisis with levothyroxine initiation. Additionally, adrenal insufficiency should be kept in mind as one of the differential diagnoses of PTH-independent hypercalcemia.

Patient Consent Statement

Verbal informed consent was obtained from the patient for publication of this case report.

Authors' Contributions

Both authors were involved in data collection, manuscript drafting, and finalizing. Both the authors have responsibility for the entire content of this manuscript.

Compliance with Ethical Principles

No ethical approval is required for single case report.

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Conflict of Interest
None declared.

References

1 Singh G, Jialal I. Polyglandular Autoimmune Syndrome Type II. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; January 2024
2 Lakhotia M, Pahadia HR, Kumar H, Singh J, Tak S. A case of autoimmune polyglandular syndrome (APS) type II with hypothyroidism, hypoadrenalism, and celiac disease - a rare combination. J Clin Diagn Res 2015;9(04):OD01–OD03
3 Dittmar M, Kahaly GJ. Polyglandular autoimmune syndromes: immunogenetics and long-term follow-up. J Clin Endocrinol Metab 2003;88(07):2983–2992
4 Kang MS, Sandhu CS, Singh N, Evans T. Initiation of levothyroxine in a patient with hypothyroidism inducing adrenal crisis requiring VA ECMO: a tale of preventable disaster. BMJ Case Rep 2019;12(08): e230601
5 Meyer G, Badenhoop K, Linder R. Addison's disease with polyglandular autoimmunity carries a more than 2·5-fold risk for adrenal crises: German Health insurance data 2010-2013. Clin Endocrinol (Oxf) 2016;85(03):347–353
6 Montoli A, Colussi G, Minetti L. Hypercalcaemia in Addison's disease: calciotropic hormone profile and bone histology. J Intern Med 1992;232(06):535–540
7 Hoener K, Sharma T. Type II polyglandular autoimmune syndrome: a case of Addison's disease precipitated by use of levothyroxine. BMJ Case Rep 2019;12(08):e230760
8 Saevik ÅB, Åkerman AK, Grønning K, et al. Clues for early detection of autoimmune Addison's disease - myths and realities. J Intern Med 2018;283(02):190–199
9 Hangaard J, Andersen M, Grodum E, Koldkjaer O, Hagen C. Pulsatile thyrotropin secretion in patients with Addison's disease during variable glucocorticoid therapy. J Clin Endocrinol Metab 1996;81(07):2502–2507
10 Agrawal S, Goyal A, Agarwal S, Khadgawat R. Hypercalcaemia, adrenal insufficiency and bilateral adrenal histoplasmosis in a middle-aged man: a diagnostic dilemma. BMJ Case Rep 2019;12 (08):e231142
11 Lee AS, Twigg SM. Opioid-induced secondary adrenal insufficiency presenting as hypercalcaemia. Endocrinol Diabetes Metab Case Rep 2015;2015:150035
12 Vasikaran SD, Tallis GA, Braund WJ. Secondary hypoadrenalism presenting with hypercalcaemia. Clin Endocrinol (Oxf) 1994;41 (02):261–264
13 De Silva SDN, Aravinthan M, Katulanda P. Glucocorticoid-induced adrenal insufficiency: an uncommon cause of hypercalcaemia. Endocrinol Diabetes Metab Case Rep 2022;2022(01): 21-0177
14 Miller SR, Kumar S, Yuile A, Menzies AM. Hypercalcaemia secondary to hypophysitis and cortisol deficiency: another immunotherapy-related adverse event. Endocrinol Diabetes Metab Case Rep 2023; 2023(01):22-0375
15 Choo KS, Yew J, Tan EJH, Puar THK. Case report: hypercalcemia as a manifestation of acute adrenal crisis precipitated by fluconazole use, and a review of the literature. Front Endocrinol (Lausanne) 2023;14:1168797

