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Primary Adrenal Insufficiency in Autoimmune Polyglandular Syndrome Type 1 - A Case Report and Literature Review

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Autoimmune Polyglandular Syndrome (APS) type 1 is a rare autosomal recessive disorder secondary to AIRE gene mutation, that is classically characterized by autoimmune hypoparathyroidism, chronic mucocutaneous candidiasis and Addison's disease. A review of the literature shows that these disease manifestations may present in any order in different age groups. Patients with APS type 1 are also at risk for other endocrinopathies. We present the case of a female patient with a history of APS type 1 and type 1 diabetes who presented with new onset hypoglycemia and decreased insulin requirement and was diagnosed with new onset adrenal insufficiency due to Addison's disease. One challenge we experienced in this patient diagnosed with concomitant autoimmune hypoparathyroidism and adrenal insufficiency was regulation of serum calcium, as cortisol replacement therapy contributes to urinary calcium loss. The goal calcium level is thus maintained at the lower limit of normal.

Keywords

APS type 1, hypoparathyroidism, primary adrenal insufficiency, Addison's disease, hypocalcemia

Conflict of Interest Statement

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CASE REPORT

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Abstract

Autoimmune Polyglandular Syndrome (APS) type 1 is a rare autosomal recessive disorder secondary to AIRE gene mutation, that is classically characterized by autoimmune hypoparathyroidism, chronic mucocutaneous candidiasis and Addison's disease. A review of the literature shows that these disease manifestations may present in any order in different age groups. Patients with APS type 1 are also at risk for other endocrinopathies. We present the case of a female patient with a history of APS type 1 and type 1 diabetes who presented with new onset hypoglycemia and decreased insulin requirement and was diagnosed with new onset adrenal insufficiency due to Addison's disease. One challenge we experienced in this patient diagnosed with concomitant autoimmune hypoparathyroidism and adrenal insufficiency was regulation of serum calcium, as cortisol replacement therapy contributes to urinary calcium loss. The goal calcium level is thus maintained at the lower limit of normal.

Keywords: APS type 1, Hypoparathyroidism, Primary adrenal insufficiency, Addison's disease, Hypocalcemia

1. Introduction

Autoimmune Polyglandular Syndrome (APS) type 1 is a rare autosomal recessive disorder secondary to AIRE gene mutation, that is classically characterized by autoimmune hypoparathyroidism, chronic mucocutaneous candidiasis and Addison's disease. A review of the literature shows that these disease manifestations may present in any order in different age groups. Patients with APS type 1 are also at risk for other endocrinopathies. We present the case of a female patient with a history of APS type 1 and type 1 diabetes who presented with new onset hypoglycemia and decreased insulin requirement and was diagnosed with new onset adrenal insufficiency due to Addison's disease. One challenge we experienced in this patient diagnosed with concomitant autoimmune hypoparathyroidism and adrenal insufficiency was regulation of serum calcium, as cortisol replacement therapy contributes to urinary calcium loss. The goal calcium level is thus maintained at the lower limit of normal.

2. Case presentation

A 46-year-old female presented to the emergency department with chief complaints of generalized fatigue, hypoglycemia, and diaphoresis. She has a history of type 1 Autoimmune Polyglandular Syndrome, type 1 diabetes mellitus, primary hypoparathyroidism, vitiligo, alopecia, chronic mucocutaneous candidiasis, primary ovarian insufficiency, and pernicious anemia. She did not have a history of adrenal insufficiency but had a positive 21-hydroxylase antibody in the past.

Three days prior to the emergency department visit, she developed gray watery diarrhea occurring multiple times throughout the day. She also endorsed loss of appetite, dysuria, polyuria, and chest discomfort. She reported frequent hypoglycemic episodes despite a significant decrease in her

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insulin regimen. She has no family history of autoimmune diseases and review of systems was otherwise unremarkable.

Vital signs were notable for a blood pressure of 98/59 mmHg. On physical examination, she was in no acute distress. Skin exam was notable for alopecia universalis, vitiligo of bilateral hands, and hyperpigmentation of the facial skin and skin of the hands and feet. Review of her driver's license photo from two years prior confirmed the hyperpigmentation. The remainder of the physical examination was normal. Basic metabolic panel revealed sodium of 143 mmol/L (136−145 mmol/L), potassium of 2.8 mmol/L (3.5−5.1 mmol/L), calcium 6.1 mg/dL (8.6−10.3 mg/dL), ionized calcium 0.83 mmol/L (1.15−1.33 mmol/L), magnesium 1.1 mg/dL (1.9−2.7 mg/dL). Thyroid function test was normal with TSH of 2.511 uIU/mL (0.450−5.330 uIU/mL).

During the hospital stay, the patient became hypoglycemic with blood glucose of 38 mg/dL. Hypoglycemia and previous positive 21-hydroxylase antibody prompted further investigation for primary adrenal insufficiency, which revealed low am cortisol of 2.5 mcg/dL (6.7−22.6 mcg/dL), positive cosyntropin stimulation (cortisol levels were 3.2 mcg/dL at 0 min, 3.7 mcg/dL at 30 min, and 3.6 mcg/dL at 60 min), and elevated ACTH 976 pg/ml (6−50 pg/ml) which were suggestive of primary adrenal insufficiency.

Her newly diagnosed adrenal insufficiency was addressed by initiating her on hydrocortisone 15 mg qAM and 10 mg qPM. Appropriate changes in the insulin regimen were also made. Multiple electrolyte derangements including hypokalemia, hypomagnesemia, and especially hypocalcemia, were challenging during the rest of the hospitalization. She was started on calcium supplements three times a day along with calcitriol with the aim to keep her calcium levels in the low normal range.

3. Discussion

Autoimmune Polyglandular Syndrome is a heterogeneous group of disorders characterized by multiple endocrinopathies. In the early 1980's it was classified into type 1 and type 2.[1] APS Type 1, also called autoimmune poly endocrinopathy-candidiasis-ectodermal dystrophy (APECED) to summarize its clinical features, is a rare disorder inherited in an autosomal recessive pattern. It is caused by a mutation in autoimmune regulator gene mutation (AIRE) located on chromosome 21q23.3. The AIRE protein is involved in thymic self-representation and immune self-tolerance.[2] Prevalence of this syndrome is estimated to be 1:80,000 and highest prevalence is found in Finland (1:25,000), Sardinia (1:14,000) and Israel (1:9000).[3] APS Type 2, also called Schmidt syndrome, is more classically characterized by adrenal insufficiency, autoimmune thyroid disease, and type 1 diabetes.[4]

Autoimmune Polyglandular Syndrome type 1 is characterized by a triad of autoimmune hypoparathyroidism, mucocutaneous candidiasis, and Addison's disease. Each component of the syndrome may take years to develop, contributing to the overall delay in the diagnosis of this syndrome. In an Italian survey on 158 patients diagnosed with APS type 1 syndrome, 93 % patients presented with one or more components of the classic triad and 7 % presented with other components. At the end of the follow up, chronic hypoparathyroidism was found as the most common manifestation (77.2 %), followed by Addison's disease (74.7 %), chronic mucocutaneous candidiasis (49.5 %), premature ovarian failure (49.5 %), autoimmune intestinal dysfunction (29.7 %), autoimmune thyroid disease (27.8 %), autoimmune gastritis/pernicious anemia (25.3 %), alopecia (24 %), and celiac disease (2.5 %).[3] Other studies have similar frequencies to the manifestations above, as well as chronic hepatitis (12−20 %), Sjogren's syndrome (12 %), keratoconjunctivitis (12−35 %), hypophysitis (7 %), and insulin-dependent diabetes mellitus (2−12 %).[5−7] This proves that the phenotype of this condition is highly variable.

The patient in this case was diagnosed with APS type 1 at an earlier stage of life. She also had a history of type 1 diabetes mellitus which is not one of the most common features of APS type 1 and is mostly associated with APS type 2. With recent frequent hypoglycemic episodes, especially fasting hypoglycemia despite decreasing insulin intake, pointed towards a new development of adrenal insufficiency. A previous work up had detected 21-hydroxylase antibodies. After diagnosis of primary adrenal insufficiency due to autoimmune Addison's disease, she started on replacement therapy with hydrocortisone 15 mg qAM and 10 mg qPM with resultant improvement of her symptoms of hypotension and hypoglycemia.

Electrolyte abnormalities were particularly challenging in this case as she presented with profound hypocalcemia, hypokalemia, and hypomagnesemia. Hypokalemia is not a common feature of adrenal insufficiency, as in adrenal insufficiency, the lack of aldosterone hormone causes potassium retention and resultant hyperkalemia.[8] However, a study has shown that only 34 % of the patients with Addison's disease develop hyperkalemia and 66 % had normokalaemia, possibly due to aldosterone

independent potassium regulation by the distal nephron.[9] In this case, co-existing diarrhea was regarded as a possible cause of gastrointestinal potassium loss.

Our patient had profound hypocalcemia with corrected serum calcium level of 6.1 mg/dL on presentation. She received aggressive intravenous and oral calcium replacement. Her low 25-hydroxy vitamin D level of 14.6 ng/ml (deficiency <20 ng/ml) had also contributed to hypocalcemia. Literature review has shown that Addison's disease is associated with hypercalcemia. This is postulated to be secondary to reduction in the filtered load and increased renal tubular calcium reabsorption. However, in this case, as the patient was non-compliant with calcium and vitamin D supplements, her calcium level was low. Subsequently after diagnosis of Addison's disease and initiation of hydrocortisone, hypocalcemia continued to persist and even became symptomatic with development of peri-oral tingling and numbness as well as carpopedal spasm. This is likely because cortisone replacement is associated with renal tubular calcium leak.[10] Due to this contradictory effect of autoimmune hypoparathyroidism and glucocorticoid replacement therapy for Addison's disease in patients with APS type 1, the goal is to achieve a low normal level of calcium. This requires regular outpatient follow-up and frequent monitoring of electrolytes.

One other interesting aspect of this case was the patient's history of a positive 21-hydroxylase antibody years before her diagnosis of adrenal insufficiency. The presence of a positive 21-hydroxylase antibody can help to detect patients with pre-clinical autoimmune adrenal insufficiency (Addison's disease). Over time, many patients go on to develop impairment of their ACTH-cortisol axis and should be monitored for development into clinically significant Addison's disease. However, no guidelines are available that state how to manage patients in this pre-clinical state. One article recommends informing patients with a positive 21-hydroxylase antibody without Addison's disease of a potential need for stress dose steroids in case of a stressful event. They also recommend following up patients with laboratory and clinical evaluation every six months to monitor for development of Addison's disease. Patients with other autoimmune diseases, such as our patient, are at higher risk than average to progress to adrenal insufficiency.[11] There are not many studies evaluating patients with positive 21-hydroxylase antibodies without Addison's disease, but one study in children with other autoimmune diseases, similar to our patient who was diagnosed with multiple of them in childhood, showed that 90 % of them progressed to Addison's disease, although the n value was very small.[12] We recommend for any patients with known APS-1 and a positive antibody titer that they follow at least every six months with laboratory and clinical evaluation as suggested above.

4. Conclusion

Autoimmune Polyglandular Syndrome type 1 is a rare genetic disorder with a mutation in the gene required for regulation of auto-reactive T-lymphocytes. Patients with this disease are at the risk of developing a number of endocrinopathies. Presence of new onset hypoglycemia and orthostatic hypotension should prompt workup for adrenal insufficiency. Due to the contradictory effect of PTH and cortisone on calcium homeostasis, regulation of serum calcium level is particularly challenging and goal calcium level should be maintained in the lower range of the normal.

Conflict of interest

The authors state there are no conflicts of interest.

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