CLINICAL VIGNETTE

Profound Hyponatremia as a Presenting Complication of Addison's Disease

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Addison's disease, also known as primary adrenal insufficiency, is a rare but often under-diagnosed disease. Though many patients are diagnosed when presenting critically ill to the hospital, the subtleties of the disease can be identified long before the patient develops overt adrenal insufficiency. Early recognition and treatment may prevent the detrimental sequelae of the disease. We present a typical presentation of Addison's disease, and discuss the proper work-up, diagnosis, and treatment of the disease. Our patient was eventually diagnosed with Schmidt's syndrome, also known as Autoimmune Polyglandular Syndrome Type II,[1,2] as the patient was found to have concomitant hypothyroidism and likely type I diabetes.

The patient is a 37-year-old male with a past medical history of Menieres disease and Vitamin D deficiency who presented to a local community hospital with severe nausea, vomiting, and abdominal pain. He was initially seen in the emergency room and was sent home with a presumptive diagnosis of antibiotic associated gastrointestinal discomfort as he had been recently treated for a sinus infection. He returned to the emergency room the next day with worsening symptoms and was admitted. His family history was notable for a mother with diabetes. His only medication was Montelukast, which he took for chronic allergic rhinitis.

At the time of presentation to the ER, his vitals were within normal limits, and a normal physical exam was documented in the record.

His admission labs were notable for a TSH of 10.5 (0.3-4.7 mcIU/mL), FT4 of 1.22 (0.8-1.6ng/dl), and a random cortisol at 14:21 noted to be <5 (<6 mcg/dL), LH 11.3 (1.8-8.6 IntU/L), FSH 6.1 (1-18 IntU/L), prolactin 20.4 (4-15.2ng/mL), testosterone 261 (240-950ng/dL), and 21-hydroxylase antibody 26 (normal <1 units/mL). His sodium was 117 mmol/L with a urine Na of 68, urine osmolality of 360, and serum osmolality of 249. A presumptive diagnosis of adrenal insufficiency was made given the low sodium and cortisol levels. The patient was started on hydrocortisone, and the following day an ACTH stimulation test was obtained while patient was still on hydrocortisone with a baseline cortisol of <5 increasing to 5.1 thirty minutes later. The patient was eventually switched to dexamethasone and repeat ACTH stimulation confirmed adrenal insufficiency. Of note, patient had reported an episode of profound hyponatremia in 2010 for which he was hospitalized and told it was likely secondary to primary polydipsia.

Per review of his hospital record, his hyponatremia was thought to be secondary to SIADH, as well as hypovolemia, and he was treated with IV fluids and tolvaptan. Given his elevated TSH, he was also started on levothyroxine 100 mcg PO daily. However, steroids were promptly stopped at the time of discharge for unclear reasons. He then presented to an outside outpatient endocrinology clinic three days later and was placed on a steroid taper. Cortisol was re-checked when patient was weaned off steroids at 1.9 and outside endocrinology notes indicated that patient may be surreptitiously using steroids. During this same visit, his A1c was found to be 6.3%. He had hyperglycemia while on high-dose steroids in the hospital. No medications or further work-up were initiated. The patient continued to have severe fatigue, nausea, and abdominal discomfort and presented to UCLA endocrinology for a second opinion.

At UCLA, his exam was notable for bronzed skin but otherwise was within normal limits. Repeat labs included an AM cortisol of 2 with stimulation to 3 after 60 minutes with a concomitant ACTH of 364 (6-95 pg/mL). TSH and FT4 were within normal limits on levothyroxine 100mcg PO daily. Given our high suspicion for Addison's disease (given previous evidence of adrenal insufficiency in the setting of a positive 21-hydroxylase antibody), a GAD antibody was checked and noted to be elevated at 101.8 (0.0-5.0 U/mL). A c-peptide was only 1.5ng/mL with a glucose of 94. We immediately started replacement steroids, hydrocortisone 20mg PO every morning and 10mg PO every evening as well as low dose fludrocortisone. Additionally, patient was started on low-dose detemir basal insulin given likely impending overt type I diabetes. Given the likelihood of Addison's disease, a CT of the abdomen was obtained and showed bilateral atrophic adrenal glands.

Repeat labs after initiation of replacement steroids showed an AM cortisol of 8 and ACTH that had down trended to 291(6-95 pg/mL).

Discussion

The severe manifestations of Addison's Disease, also known as Primary Adrenal Cortical Deficiency, does not make itself clinically apparent until the majority (at least 90%) of the adrenal cortical tissue has been compromised. This could explain why our patient was initially found to have a low sodium in 2010 and went on 6 more years before exhibiting the severe manifestations of the disease. In centuries past,

tuberculosis was one of the most common causes of adrenal cortical tissue destruction. This was the case when Dr. Thomas Addison first described the disease at Guy's Hospital, London, England in 1855. Today, the majority of cases are due to autoimmune destruction of cortical tissue. Proopiomelanocortin elevation occurs due to the feedback loop from the adrenal gland to the pituitary gland being essentially shut off. This molecule is then cleaved into melanocyte stimulating hormone (MSH) as well as ACTH. It is the increase in MSH that causes excess melatonin deposition and bronze skin tone classic in patients with Addison's disease. Indeed, our patient had a positive21-hydroxylase antibody, which supports this theory.

As occurred in our case, care must be taken in following these patients after their hospitalization. This patient was assumed to have secondary adrenal insufficiency and was started on a steroid taper by an outside endocrinologist. Unfortunately, a cortisol level was used erroneously to evaluate treatment response rather than ACTH, which would have been high in this patient.

In secondary adrenal insufficiency, ACTH should start to rise as cortisol is being weaned and a concurrent ACTH should be drawn for these cases.

Generally, ACTH levels can be checked periodically to assess treatment effect in Addison's disease, but normalization of ACTH is not necessarily the goal of therapy. It is not helpful to follow ACTH in patients with secondary adrenal insufficiency as the levels are always low regardless of time of day. However, in primary adrenal insufficiency, a low normal ACTH would indicate over-replacement of cortisol, and a recommendation to lower the cortisol replacement. Arit W et al[3] measured cortisol levels 60-300 minutes after taking hydrocortisone 25mg and found no significant correlation to clinical measures of symptoms such as fatigue and reduced strength at varying times during the day. This suggests measuring cortisol levels in patients on cortisol therapy is not very useful in adjusting dose. Generally, clinical assessment has been used by practitioners as the best gauge in dosing cortisol in Addison's patients.

This case demonstrates several important teaching points. First, an ACTH stimulation test cannot be properly interpreted when patients are on hydrocortisone. Additionally, adrenal insufficiency should always be considered in a patient with repeated profound hyponatremia.[4] More importantly, patients with a presumptive diagnosis of Addison's disease or any form of adrenal insufficiency should never have immediate cessation of steroids, and in fact, patients with Addison's disease need to be on life-long steroids. Lastly, it is important to evaluate and treat the co-morbidities associated with Addison's disease including Type I DM and hypothyroidism, as well as other suspected auto-immune diseases. Luckily, this patient had no major clinical complications from a delayed diagnosis. This case serves to remind us of when to suspect Addison's disease and how to manage its acute and chronic complications.

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