

## CLINICAL VIGNETTE

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# An Inpatient Approach to Adrenal Insufficiency: A Case Report and Discussion

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### *Introduction*

Adrenal insufficiency is a disorder with a plethora of potential causes which can present with a wide range of symptoms and severities, from shock to minor non-specific complaints such as nausea and fatigue. Given this broad range of causes and presentations, adrenal insufficiency should be commonly considered on differential diagnoses for hospitalized patients with a broad scope of chief complaints. Early recognition and treatment is important to limit morbidity. Hospital clinicians should be aware of its myriad presentations to keep it on their differentials, and comfortable enough with its workup and treatment to approach it efficiently.

We present a patient with common and somewhat vague complaints, noted to have electrolyte abnormalities, and subsequently diagnosed with central (or secondary) adrenal insufficiency. We thereafter discuss the multitude of potential causes of adrenal insufficiency, its range of clinical manifestations, evidence-based approach to workup, and initial treatment considerations.

### *Case Report*

A 78-year-old female with meningioma status post prior radiation and recent partial resection presented to the emergency department with 3-4 days of nausea and 1-2 days of persistent emesis with increasing difficulty tolerating oral intake. She also reported general fatigue, attributed by the patient to inability to eat enough. She noted no new focal weakness or change in mentation or sensation.

The patient had history of migraine, depression and left sphenoid meningioma. This was diagnosed two years prior, after presenting with left proptosis. She had left third nerve palsy which was not amenable to surgical correction and underwent radiation. Radiation was completed about 18 months prior to presentation. Given proximity of the meningioma to the pituitary, she was monitored for hypopituitarism. Periodic lab studies as recent as two months prior to presentation were consistent with normal pituitary function.

About one month prior, the patient was admitted for elective craniotomy with meningioma debulking (complete resection was not possible due to anatomical considerations). This was uncomplicated and well-tolerated. The post-operative course was notable for asymptomatic hyponatremia, attributed to the syndrome of inappropriate ADH release due to the neurosurgi-

cal procedure. This resolved with medical treatment including fludrocortisone and salt tablet supplementation. The patient was discharged to an acute rehabilitation hospital, where she satisfactorily completed a full course. Sodium normalized, and fludrocortisone and salt tablets were stopped. The patient was discharged to home approximately two weeks prior to the current presentation. She had subsequently done well until the most recent 3-4 days.

On arrival to the emergency department the patient was afebrile, with blood pressures slightly lower than her baseline (systolic pressures were in 90 mm Hg range, whereas typical baseline for patient was 100-120 mm Hg) and heart rate in 90s range. Initial laboratory studies were notable for a sodium of 126 mmol/L, down from 139 mmol/L two weeks prior. Potassium was normal. Urine electrolytes were notable for normal urine sodium (44 mmol/L) and osmolality (411 mOsm/Kg). CT of the abdomen and pelvis showed no acute pathology. The patient was admitted for continued medical care. A repeat MRI brain was performed, showing some slightly increased bulk of residual meningioma.

Pituitary hormone studies were evaluated, the morning after admission. Morning cortisol was 3 mcg/dL (low) and ACTH was 4 pg/mL (borderline low). TSH was 0.62 mIU/mL (in normal range), but with low free T4 (0.4 ng/dL). LH and FSH were in normal range. Endocrinology consultation felt the patient had likely central (secondary) adrenal insufficiency and possibly early central hypothyroidism. Given clinical context, this was attributed to her known meningioma. Further serologic investigation (such as cosyntropin stimulation testing) was felt to be unnecessary. Neurosurgery was consulted, and patient elected to pursue non-surgical management.

The patient was initiated on physiologic doses of oral hydrocortisone at the direction of endocrinology. She was additionally started on levothyroxine supplementation. Her nausea subsequently improved, and she was able to tolerate oral intake. Sodium improved over the subsequent several days and she felt more energetic and was able to ambulate similarly to her baseline. She was discharged home by hospital day four.

### *Discussion*

Adrenal insufficiency due to insufficient adrenal corticosteroid, mineralocorticoid, and/or androgen secretion, can be caused by

diseases of the adrenal gland itself (termed primary adrenal insufficiency), interference with corticotropin (ACTH) secretion by the pituitary gland (termed secondary adrenal insufficiency), or interference with corticotropin-releasing hormone (CRH) secretion by the hypothalamus (termed tertiary adrenal insufficiency).

Primary adrenal insufficiency, also known as Addison's disease, is the most common pathology, but is quite rare, with prevalence ranging from 39-144 cases per million population.<sup>1</sup> The most common etiology of primary adrenal insufficiency is autoimmune adrenal destruction, which is responsible for up to 70-90% of cases.<sup>2</sup> Approximately 50-65% of patients with autoimmune adrenal disease also have one or more other autoimmune endocrine disorders, including type 1 diabetes mellitus, Graves' disease, or chronic autoimmune thyroid disease.<sup>1,2</sup> Other causes of primary adrenal insufficiency can include infections (such as tuberculosis, disseminated fungal infection, HIV, syphilis, and African trypanosomiasis), metastatic cancer, adrenal hemorrhage or infarction, medication-induced damage (including fluconazole, rifampin, phenytoin, among others).<sup>3-5</sup>

Secondary and tertiary adrenal insufficiency are caused by any disease process affecting the normal secretion of ACTH by the pituitary or CRH by the hypothalamus. Secondary causes, which involve lack of pituitary ACTH secretion precipitating inadequate adrenal stimulation, include mass effect from pituitary tumors (as in our case), infectious diseases (such as tuberculosis and histoplasmosis), pituitary infarction, and head trauma.<sup>6</sup> Tertiary causes involve reduction in CRH secretion, leading by cascade to inadequate ACTH release and subsequently poor adrenal stimulation. This is most commonly precipitated by abrupt cessation of high dose glucocorticoid administration, or following the correction of Cushing's syndrome. In each of these cases, exposure to supraphysiologic corticosteroid levels for prolonged time periods leads the hypothalamus to decrease production of CRH. When the situation is abruptly reversed, the hypothalamus is unable to quickly adjust.<sup>7</sup>

Adrenal insufficiency can present in multiple different ways with widely varying severity depending upon acuity of development, extent of deficiency, and ultimate cause of deficiency (for example central adrenal insufficiency, as in our case, presents somewhat differently from primary adrenal insufficiency).

Symptoms of less acute, more indolent early insufficiency are quite nonspecific. These classically include fatigue (in 85-94% of patients), loss of appetite (53-67%), weight loss (66-76%), nausea, vomiting, and abdominal pain (49-62%), and joint pain (36-40%).<sup>8</sup> The most common laboratory abnormality is hyponatremia (in 70-80% of patients), followed by hyperkalemia (30-40%), and normocytic anemia (11-15%).<sup>8</sup> Of note, in secondary adrenal insufficiency, electrolyte disturbances are less frequent, because the mineralocorticoid axis is typically intact; however, hyponatremia is still commonly seen because of decreased inhibition of ADH caused by lack of cortisol

activity.<sup>8</sup> Evaluation of hyponatremia in these cases will commonly show inappropriately normal urine sodium and osmolality, similar to cases of the syndrome of inappropriate ADH release (SIADH). A classic physical exam finding associated with primary adrenal insufficiency is skin hyperpigmentation (seen in 41-74% of patients), which is caused by excess ACTH leading to increased activation of melanocortin 1 receptors.<sup>8</sup> This is not seen in secondary adrenal insufficiency, in which ACTH is deficient rather than excessive.

Because of the non-specificity nature of these more indolent presentations, there is commonly a delay to diagnosis. A 2010 cross-sectional study suggested that less than 30% of women and 50% of men ultimately found to have adrenal insufficiency were diagnosed within the first 6 months of symptom onset and 20% of patients had symptoms for 5 years or more prior to diagnosis.<sup>9</sup>

In this setting of non-specific early symptoms and common diagnostic delays, patients are often diagnosed in the setting of adrenal crisis. Acute adrenal crisis is generally precipitated in setting of existing adrenal insufficiency by development of an additional acute problem. Classically, a patient with adrenal insufficiency exposed to a new stressor such as acute infection or following a trauma or surgical procedure can develop acute crisis, as their adrenal function is not able to provide typical "stress dose" of cortisol needed to meet physiologic needs demanded by the event.<sup>10</sup> The hallmark manifestations of adrenal crisis are dehydration, hypotension, and shock out of proportion to any concurrent known illness.<sup>11</sup> Patients also commonly have other symptoms, including unexplained hypoglycemia, unexplained fever, acute abdominal pain with or without nausea and vomiting.<sup>11</sup> Without early intervention, the situation can be life-threatening.

Because of the non-specific presentation, making a diagnosis of adrenal insufficiency requires a high index of suspicion. If suspicion is present, the first diagnostic step is to determine whether inappropriately low serum cortisol is present. This can be tested most efficiently with a morning serum cortisol level (ideally measured between 8 and 9 am).<sup>12</sup> A morning cortisol level over 19 ug/dL effectively rules out adrenal insufficiency and a level under 3 ug/dL effectively rules in adrenal insufficiency.<sup>12</sup> Levels between 4-19 require additional testing, typically a 250 mcg corticotropin stimulation test, in which plasma cortisol is measured before administration and again 30-60 minutes after administration of corticotropin.<sup>12</sup> The test is considered normal if cortisol level following administration is over 20 ug/dL; the test is abnormal if the cortisol level fails to rise following stimulation. Other testing such as salivary cortisol have been studied, but are not well-validated and their use on hospitalized patients is less appropriate.<sup>12</sup> Likewise, given the physiologic daytime variation of cortisol levels, single-measurement cortisol levels are only interpretable when drawn in the morning.<sup>12</sup>

Once a diagnosis of adrenal insufficiency is confirmed, the next step is establishment of the level of defect within the hypo-

thalamic-pituitary-adrenal axis (i.e. primary vs secondary vs tertiary insufficiency). Plasma corticotropin (ACTH) level, commonly checked at the same time as a corticotropin-stimulation test, is often sufficient.<sup>12</sup> Primary adrenal insufficiency will be characterized by high ACTH levels, whereas secondary and tertiary insufficiency will involve low or inappropriately normal ACTH levels.<sup>12</sup>

In the case of mild or early secondary adrenal insufficiency, equivocal results can be seen. In this instance, either the insulin tolerance test or metyrapone test may be indicated for further investigation.<sup>12</sup> The insulin tolerance test monitors physiologic stimulation of cortisol release in setting of insulin-induced hypoglycemia.<sup>13</sup> This test is limited by need for extensive monitoring and unpleasantness to the patient. The metyrapone test involves administration of metyrapone, which blocks the last step in cortisol synthesis (from 11-deoxycortisol to cortisol), artificially lowering serum cortisol.<sup>12</sup> Following metyrapone administration, serum 11-deoxycortisol level and serum ACTH are measured – in the case of normal patients the levels will rise significantly, whereas in setting of adrenal insufficiency they will not rise or will rise only marginally.<sup>12</sup> Given the complexity of administration of these tests, their use is best accomplished with endocrinological consultation.

Distinguishing between secondary and tertiary adrenal insufficiency can commonly be accomplished using clinical context. However, if necessary, a corticotropin-releasing hormone (CRH) stimulation test can be performed. Following administration of CRH, patients with tertiary adrenal insufficiency will have a large increase in ACTH levels, whereas those with secondary adrenal insufficiency will have little to no response.<sup>14</sup>

Once the level of axis defect is known, a final diagnostic step is determination of ultimate cause of the pathology. For primary adrenal insufficiency, workup will likely involve abdominal imaging, measurement of autoantibodies to evaluate for autoimmune cause, and consideration of tissue sampling and further infectious workup as indicated by context.<sup>15</sup> Determining the cause of secondary or tertiary adrenal insufficiency will typically involve brain imaging initially, with further workup guided by clinical context.

The treatment of adrenal insufficiency is aimed at replacing the deficient hormones. The backbone of treatment is corticosteroid replacement, with the goal being mimicry of normal diurnal cortisol rhythm. A common regimen involves hydrocortisone, dosed two or three times daily, dosed as low as possible to maintain symptom relief.<sup>15</sup> Patients with primary adrenal insufficiency will also often require mineralocorticoid replacement to prevent sodium and intravascular volume loss as well as hyperkalemia. Hydrocortisone has some mineralocorticoid activity, but patients commonly also receive an agent such as fludrocortisone, typically dosed daily.<sup>15</sup> Likewise, with primary adrenal insufficiency, some patients (especially female patients) have been noted to have decreased mood and quality of life, which is suspected to be related to androgen deficiency.

In these cases, supplementation with daily DHEA has been shown to have modest benefits in mood and quality of life.<sup>16</sup>

Finally, a mainstay of long-term treatment of adrenal insufficiency involves patient and family education, with special importance placed upon recognition of risks and limitations of long-term replacement regimens. Even with adequate long-term regimens, patients will remain at constant risk for adrenal crisis should they develop additional stress-related situations, including infections, surgical procedures, and traumas. It is imperative that patients and their families understand this risk and how to mitigate it. With minor infections, patients can often independently increase steroid dosing for short periods of time to mimic adrenal stress response.<sup>15</sup> In other more severe instances, patients may require physician-guided dose adjustment. In the setting of acute hospitalization, treatment teams will commonly need to provide stress-doses of steroids as indicated by the clinical context.<sup>15</sup>

### Conclusion

Our patient was seen as an outpatient by endocrinology two weeks following discharge. She continued to tolerate oral intake and denied recurrent nausea. Likewise, her energy had continued to improve. Lab studies showed normalization of free T4 (adrenal axis was not re-checked given symptom resolution). The patient was also seen by her oncologist, and given enlargement of residual disease elected to start chemotherapy.

Our patient presented with vague and largely mild symptoms related to early secondary adrenal insufficiency. These included nausea and vomiting, as well as fatigue. Laboratory studies indicated new hyponatremia, and urine studies showed inappropriately normal urine sodium and osmolality. Her morning serum cortisol was low, with borderline low ACTH, consistent with secondary cause. Given high clinical suspicion given context, the adrenal insufficiency was recognized with a minimum of diagnostic delay, and the patient was able to be effectively treated with medical supplementation. She will require continued surveillance of symptoms and laboratory studies to guide future treatment adjustments, and will need to be continuously aware of the risks associated with adrenal insufficiency.

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