Approach to Adrenal Insufficiency

Developed by Rebecca Quilty and Dr. Heather Power for PedsCases.com.
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Hi! My name is Rebecca Quilty and I'm a fourth-year medical student from Memorial University. This podcast was developed with Dr. Heather Power, a Pediatric Endocrinologist at Memorial University. Today, I will discuss the topic of adrenal insufficiency. This podcast will have the following objectives:

1. To describe the general physiology of adrenal cortex hormones.
2. To list and elaborate on the etiologies of primary and secondary adrenal insufficiency, with emphasis on congenital adrenal hyperplasia.
3. To discuss an approach to the evaluation of a patient with adrenal insufficiency using a clinical example.
4. To outline the diagnostic process of adrenal insufficiency and important details in management.

Let's begin this podcast with a brief review of adrenal hormone physiology. The hypothalamus-pituitary-adrenal (HPA) axis is one of the main pathways in the stress response. Inputs from normal circadian rhythm and times of stress cause the hypothalamus to release corticotropin releasing hormone (CRH) into the hypophyseal portal system, or the system of blood vessels connecting it to the anterior pituitary gland. In response to CRH, the anterior pituitary gland secretes adrenocorticotropin hormone (ACTH) that acts upon the adrenal glands located above the kidneys. The adrenal glands will secrete the glucocorticoid cortisol from the adrenal cortex. Cortisol orchestrates a wide range of effects that help in the stress response. It is a counter-regulatory hormone that raises blood glucose levels by stimulating gluconeogenesis, it alters the metabolism of protein and fat, and it is involved in a host of other functions including maintaining or raising blood pressure, exerting anti-inflammatory effects, and maintaining a state of arousal. When cortisol levels rise, cortisol inhibits the function of CRH and ACTH through a negative feedback loop to maintain homeostasis and prevent excess cortisol from accumulating.

The adrenal cortex also produces mineralocorticoids, namely aldosterone. Aldosterone plays an important role in electrolyte and fluid balance. The renin-angiotensin-

aldosterone system (RAAS) originating in the kidneys regulates the synthesis of aldosterone in response to a decrease in blood pressure or intravascular fluid volume. The juxtaglomerular apparatus near the glomeruli secrete renin that stimulates the conversion of angiotensinogen to angiotensin I. Angiotensin-converting enzyme then converts angiotensin I to angiotensin II, which in turn stimulates the adrenal cortex to produce aldosterone. Aldosterone works on the distal tubules and collecting ducts of the kidney to increase the reabsorption of sodium and water, and increase the secretion of potassium, thus elevating blood pressure.

Adrenal insufficiency is a condition in which the secretion of glucocorticoids and mineralocorticoids from the adrenal glands is impaired. It can have life-threatening consequences when the presentation leads to an acute adrenal crisis, resulting in cardiovascular and hemodynamic collapse. If not promptly identified and managed appropriately, it can progress quickly to cause significant morbidity such as a coma and even death. Death results in one in every 200 cases of adrenal crises. Thankfully, this condition is relatively rare in the pediatric population, but it can present initially with non-specific signs and symptoms, thus necessitating a high index of suspicion for this presentation and an awareness among pediatricians.

Let's begin with introducing a case.

You are a fourth year medical student doing a Pediatric Emergency rotation. You are asked to see a 9-day old baby boy that has presented with vomiting. History reveals a 2-day history of decreased feeding and irritability with 2 episodes of vomiting today. He has had only one wet diaper in the past 24 hours. There is no history of fever or sick contacts. He was born by vaginal delivery at term weighing 3.5 kg after an uncomplicated pregnancy with an otherwise unremarkable postnatal period. He had initially been feeding well for the first week of life. On exam, he was mildly hypotensive, mildly tachycardic and weighed 3.2 kg. He had dry mucous membranes and a cap refill of 3 seconds. His fontanelle was soft and flat. You noticed some areas of hyperpigmentation around his axilla and groin. The remainder of his exam was unremarkable. Initial investigations yielded a Na of 131 mmol/L, a K of 5.9 mmol/L, and a glucose of 2 mmol/L.

Etiology of Adrenal Insufficiency

Adrenal insufficiency can result from many etiologies. It is broadly classified into two groups: primary and secondary adrenal insufficiency. Primary adrenal insufficiency is insufficient glucocorticoid secretion due to a problem with the adrenal gland. Mineralocorticoid secretion may or may not be affected as well. Secondary adrenal insufficiency is a decrease in function of the adrenal cortex due to a deficiency in CRH or ACTH, thus at the hypothalamic or anterior pituitary level. In secondary adrenal insufficiency, mineralocorticoid production is unaffected.

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Primary adrenal insufficiency classification can be further broken down into congenital and acquired sub-categories. In primary congenital adrenal insufficiencies, there are several groups of etiologies: impaired steroid hormone biosynthesis (ex: congenital adrenal hyperplasia (CAH), cholesterol synthesis or metabolism defects), adrenal destruction or dysfunction (ex: mitochondrial defects, and defects in lipid metabolism), and impaired adrenal development or adrenal hypoplasia. Some acquired primary adrenal insufficiency causes are infection (ex: tuberculosis, HIV, CMV), hemorrhage or infarction of the gland, drug side effects (ex: ketoconazole, rifampin), and autoimmune adrenalitis (Addison's disease).

Causes of secondary adrenal insufficiency can include suppression of ACTH secretion due to long-term exogenous glucocorticoid usage, infiltrative process (ex: craniopharyngioma, sarcoidosis), radiation therapy, multiple anterior pituitary hormone deficiency, and hypothalamic dysfunction. The discussion of all these etiologies is beyond the scope of this podcast, but I will focus on the most common etiology of CAH.

CAH is a group of disorders characterized by mutations in enzymes involved in the biosynthesis of adrenal glucocorticoids. By far the most common enzymatic defect, occurring in 90-95% of cases, is a defect in 21-hydroxylase. This enzyme has roles in the synthesis of both cortisol and aldosterone. It converts 17-hydroxyprogesterone to 11-deoxycortisol upstream in the cortisol synthesis pathway, and progesterone to 11-deoxycorticosterone upstream in the aldosterone synthesis pathway. When 21-hydroxylase is deficient, there is inadequate cortisol being produced, which triggers an increase in ACTH to stimulate the adrenal cortex. This increase in ACTH stimulation causes a build-up in precursors in these biosynthetic pathways, which become shunted towards the other avenue in the pathway: androgen production. The resulting state of hyperandrogenism causes virilization in girls, which may present as genital ambiguity in a female infant, and an increase in growth velocity in both sexes in early childhood. Adult height can, however, be compromised as there is early fusion of the epiphyseal growth plates. The hyperandrogenism can also cause an early development of pubic hair and acne in childhood. Up to 75% of patients will also have a deficiency in aldosterone and may present with a salt-wasting crisis: significant hyponatremia, dehydration, and possible shock. It is important to note that I have discussed the classical form of this enzyme deficiency. A non-classical form also exists with a less severe presentation, as 20-60% of the enzyme activity may remain.

Clinical Assessment of Adrenal Insufficiency

When assessing a patient with adrenal insufficiency, the clinical presentation can be vastly different based on if the adrenal insufficiency is acute or chronic. In acute adrenal insufficiency or an adrenal crisis, the presentation can be a medical emergency necessitating first an ABC assessment to ensure the patient is stable followed by resuscitation, with further discussion on this later in the podcast. They can present with severe dehydration, hypotension, an altered mental status, and even seizures. Important elements to ask on history would include asking about an inciting event or

stressor, such as an illness, recent surgery or trauma. Infants can also present in the second week of life with acute adrenal insufficiency with a decrease in feeding, weight loss, and lethargy.

In chronic adrenal insufficiency, the presentation can be more non-specific. Children can present with a history of chronic fatigue, a decrease in appetite, nausea, vomiting, abdominal pain, and salt-craving. It is important to ask about any changes in behavior as adrenal insufficiency can cause mood changes, specifically depression. Hyperpigmentation of the skin can also occur. Hyperpigmentation occurs due to an increase in melanocyte stimulation hormone (MSH) secretion, as MSH and ACTH have a common precursor molecule: pro-opiomelanocortin. Pro-opiomelanocortin increases with low cortisol levels, thus increasing both ACTH and MSH. Asking about the presence of pubic and axillary hair and acne in children and adolescents is crucial. Adrenal insufficiency due to CAH can lead to early development of pubic hair in children due to the hyperandrogenic state, but there can be a decrease in pubic or axillary hair in adolescents in other causes of adrenal insufficiency. Determining if there was a history of genital ambiguity in females is also important when considering CAH.

Other important elements on history include asking about symptoms of other pituitary hormone dysfunction such as delayed puberty in older children and adolescents, decreased growth velocity, symptoms of hypothyroidism (ex: cold intolerance, constipation, fatigue, weight gain), and diabetes insipidus (ex: polyuria or polydipsia). As well, asking about headaches and changes in vision to rule out an intracranial tumour should not be missed.

In terms of medication history, it is important to ask about exogenous glucocorticoid usage. Be sure to include all routes of administration of glucocorticoids, specifically inhaled or topical glucocorticoids. It is also important to ask if the patient is taking their glucocorticoids as prescribed, as any sudden discontinuation, if the HPA axis is suppressed, could lead to an adrenal crisis.

On exam, it is first important to check vitals to make sure the patient is stable, paying attention to look for hypotension or tachycardia. It is also important to check for orthostatic hypotension which may be an earlier sign of a decrease in vascular tone or of dehydration. Measure their height and weight and plot their percentiles, comparing to previous measurements if available. Assessing for clinical signs of dehydration such as a sunken fontanelle, dry mucous membranes, skin turgor, and capillary refill is also important. Be sure to assess skin and mucosa for any areas of hyperpigmentation, especially in skin creases and genitalia. Assess the genitalia in female infants for virilization. Also be sure to complete a general cardiac, respiratory, and abdominal exam.

Initial investigations should include measuring electrolyte levels as patients with adrenal insufficiency will often be hyponatremic and hyperkalemic. Checking serum glucose

levels to look for hypoglycemia is also important. A blood gas should be done to assess for metabolic acidosis.

Diagnosis of Adrenal Insufficiency

When adrenal insufficiency is suspected, the diagnosis involves confirming low cortisol levels, determining if the adrenal insufficiency is primary or secondary, and determining the cause.

Initial screening involves a serum cortisol level drawn early in the morning. Cortisol is secreted on a circadian rhythm with its highest levels in the early morning. A decreased cortisol level at that time would be abnormal. An early morning serum ACTH level can also be conducted to elucidate if it is primary or secondary adrenal insufficiency. A low serum cortisol level (< 138 nmol/L) combined with an elevated serum ACTH level (> 100 pg/mL) would provide evidence of primary adrenal insufficiency. If the early morning cortisol level is low, but the ACTH level is also low, then this would be more representative of a secondary adrenal insufficiency. This initial screening is limited in infants and in early childhood however, as the HPA axis may be immature and an established circadian rhythm might not yet be developed.

The initial testing is often confirmed by an ACTH stimulation test to make the diagnosis of adrenal insufficiency. This test involves the IV administration of high dose synacthen, a synthetic ACTH. Serum cortisol levels are measured just before administration, 30 minutes after administration, and 60 minutes after administration. A normal test would show a rise in cortisol with the administration of synthetic ACTH. A normal cortisol peak would measure between 500-550 nmol/L and there should be a 2-3 fold increase in cortisol levels. The ACTH stimulation test does not differentiate between primary and secondary adrenal insufficiency, as it can be abnormal in both situations. An assessment of mineralocorticoid function can, however, be helpful to decipher between primary and secondary adrenal insufficiency. Mineralocorticoid levels will always be normal in secondary adrenal insufficiency, as it is regulated by RAAS and not the HPA axis. To assess mineralocorticoid levels, plasma renin activity levels, which measure the production of angiotensin I from angiotensinogen, and the plasma renin: aldosterone ratio can be measured. An elevated plasma renin activity level or an elevated plasma renin to aldosterone ratio can indicate a mineralocorticoid deficiency, further confirming primary adrenal insufficiency over a secondary cause. It is important to note that a mineralocorticoid deficiency is not always present in primary adrenal insufficiency.

Once adrenal insufficiency has been established, the etiology must be determined, and further investigations will depend on the clinical picture. If CAH is suspected, it can be confirmed with testing 17-hydroxyprogesterone levels in the serum, which would be elevated in CAH. Also, the measurement of androgen levels (ex: DHEAS, androstenedione) can help confirm CAH. Androgen levels would be elevated in CAH but decreased in other causes of adrenal insufficiency. Several provinces also include CAH as a condition tested in their newborn screening program through the measurement of

17-hydroxyprogesterone levels in dried blood spots. The goal of this screening program is to decrease the time to diagnosis, especially in newborn males presenting with a salt-wasting crisis, and improve outcomes. This test, however, is not perfect and factors such as gestational age, illness, or stress can lead to many false positive results, which has limited its universal uptake in the newborn screening program. If considering an autoimmune etiology, screen for other autoimmune conditions. This may include measuring tissue transglutaminase and IgA for celiac disease, anti-thyroid peroxidase antibodies for Hashimoto's thyroiditis or Grave's disease, and screening for type 1 diabetes. As well, if specifically wanting to test for autoimmune adrenalitis, elevated 21-hydroxylase antibodies in the serum is a common finding. If considering secondary adrenal insufficiency, other pituitary hormone function should be assessed including thyroid stimulating hormone, luteinizing hormone, follicular stimulating hormone, and insulin-like growth factor (as a measurement of growth hormone function). Should concerns be raised about an intracranial tumour, brain imaging such as an MRI can also be obtained.

Treatment of adrenal insufficiency

The goals of adrenal insufficiency therapy include reducing the signs and symptoms of low cortisol levels, preventing adrenal crises, and normalizing growth and pubertal development. The mainstay of the treatment of adrenal insufficiency is glucocorticoid replacement, and in some cases of primary adrenal insufficiency, mineralocorticoid replacement. Glucocorticoid replacement in children is through the administration of hydrocortisone, as it has less of a suppressive effect on growth compared to prednisolone or dexamethasone. Hydrocortisone has a short half-life requiring three daily dosages. In CAH, the dosage of hydrocortisone is higher than in other causes of adrenal insufficiency in order to suppress the excess adrenal gland stimulation by ACTH and CRH, as well as to decrease the elevated adrenal androgens. For those who are also mineralocorticoid deficient, treatment with fludrocortisone is required. Sodium chloride supplementation is also recommended in salt-wasting for infants up to 8-12 months, as breast milk and formula do not contain enough salt to maintain their requirements.

In the case of an adrenal crisis**,** acute emergent management is necessary as it can be life-threatening and cause significant morbidity. Patients can quickly deteriorate with a rapid development of hypotension and hypoglycemia, emphasizing the need to rapidly identify a patient in adrenal crisis and initiate the resuscitation effort emergently**.** Prompt fluid resuscitation with intravenous isotonic normal saline boluses is important to maintain hemodynamic status. Further fluid replacement can then be resumed with an isotonic solution containing dextrose, typically 5% dextrose in normal saline (D5NS), to normalize serum glucose concentrations. One dose of hydrocortisone at 100 mg/m^2 either intravenously or intramuscularly should be given emergently to normalize cortisol levels and then 100 mg/m^2/day after that. It is important to monitor potassium levels closely in the setting of hyperkalemia, with cardiac monitoring. If hyperkalemia is severe or causing symptoms, then treatment may be considered. Treatment of hyperkalemia

could include the stabilization of cell membranes using IV calcium gluconate, shifting potassium intracellularly using glucose then insulin, or stimulating potassium excretion using diuretics or a potassium-binding resin like kayexalate. Management in an intensive care setting is necessary to monitor hemodynamic status and response to resuscitation.

Let's return to our case.

Resuscitation efforts were started promptly by the team with IV normal saline boluses and hydrocortisone. Fluid replacement was then continued with D5NS and his fluid status, electrolytes, and glucose levels subsequently normalized. He was admitted for further observation and investigations. The following day he was started on fludrocortisone and sodium chloride supplementation. Subsequent testing revealed an elevated 17-hydroxyprogesterone, confirming the diagnosis of congenital adrenal hyperplasia. His family heard about some of the negative side effects associated with prolonged steroid treatment and is concerned about the prognosis of this diagnosis and implications of treatment.

Long-term management of adrenal insufficiency and CAH

A crucial area of education for this family with this new diagnosis is the importance of stress dosing in the setting of illness, trauma or surgery. Prolonged treatment with exogenous glucocorticoids downregulates the HPA axis and it will not respond appropriately to situations of stress, where typically it would be triggered to increase the secretion of cortisol. The usual dosage of hydrocortisone must therefore be increased in illnesses with fever, vomiting, diarrhea, or inadequate oral intake to double or triple the usual dose. If oral glucocorticoids are not tolerated, then an intramuscular injection of hydrocortisone is needed, and they should present for medical care. Caregivers are given an action plan that clearly describes the management of sick days and when to present for urgent medical care. All patients should also have a medic alert bracelet or necklace stating their diagnosis of adrenal insufficiency and the need for hydrocortisone treatment.

It is also important to monitor for any adverse effects of excess glucocorticoids. These could include obesity, striae, poor growth, hypertension, decreased bone mineral density, and glucose intolerance. If these signs or symptoms are observed, the dosage of glucocorticoids may be too high or may not adequately reflect the physiological circadian rhythm.

Response to treatment in CAH is often measured through monitoring biochemical markers, growth velocity, and bone age. The biochemical markers that are measured include 17-hydroxyprogesterone, testosterone, and androstenedione serum levels. An acceleration in growth velocity or an advanced bone age indicates undertreatment of CAH. Measuring plasma renin activity regularly is also important to gauge effectiveness of mineralocorticoid replacement therapy.

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Let's review some of the main points of this podcast.

1. The adrenal cortex produces both glucocorticoids and mineralocorticoids that are important in the stress response and in electrolyte and fluid balance, respectively.
2. Adrenal insufficiency is an impairment of the secretion of glucocorticoids from the adrenal cortex and can be caused by a primary defect in the adrenal gland itself, or a secondary defect caused by a decrease in function of the pituitary gland or hypothalamus.
3. Adrenal insufficiency presentations can range from an adrenal crisis with a high risk of serious morbidity or sudden death to a non-specific history of fatigue, weight loss, anorexia and nausea, necessitating a high index of suspicion amongst clinicians.
4. The diagnosis of adrenal insufficiency is based upon the principles of confirming the cortisol deficiency through early morning serum cortisol levels and then an ACTH stimulation test, determining whether it is primary or secondary through assessing an early morning serum ACTH level and the presence of a mineralocorticoid deficiency, and determining the etiology with further investigations depending on the clinical picture.
5. The treatment principles of adrenal insufficiency include the replacement of glucocorticoids and mineralocorticoids, preventing adrenal crises, monitoring for any adverse effects to treatment, and ensuring normal pubertal growth and development.

Thanks for listening!

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