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Educational Case

Educational Case: Adrenocortical insufficiency—Causes and pathogenesis

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see https://www.journals.elsevier.com/academic-pathology/news/pathology-competencies-for-medical-education-pcme.[1]

Keywords: Pathology competencies, Organ system pathology, Endocrine, Hypoadrenalism, Primary adrenal insufficiency, Secondary adrenal insufficiency, Acute adrenal insufficiency, Chronic adrenal insufficiency

Primary objective

Objective EN4.4: Adrenocortical insufficiency: Compare and contrast the causes of adrenocortical insufficiency, including the pathogenesis of primary acute and chronic adrenocortical insufficiency.

Competency 2: Organ system pathology; Topic EN: Endocrine; Learning goal 4: Hyper- and hypoadrenalism.

Patient presentation

A 9-year-old girl with a history of asthma, celiac disease, and frequent "stomach aches" presents to an urban emergency department with a 5-day history of abdominal pain. She is accompanied by her mother. She complains of waxing-and-waning generalized abdominal pain, poor appetite, and fatigue for 5 days. She also complains of vomiting and subsequent dry heaves that began the morning of the presentation. She has been unable to keep down fluids today. Additionally, she reports having a sore throat and fever for four days. She has had frequent urination but denies pain or burning with urination.

A review of systems reveals chronic bilateral distal leg pain that radiates to the knees and has been present for years. She says that ibuprofen provides relief. The patient denies any chills with her fever, denies headache or dizziness, reports no changes in hearing or vision, and denies chest pain or shortness of breath. The patient reports no diarrhea or constipation. There is no history of blood in stools.

The mother states that the patient had a similar episode six months ago at which time she was admitted to the hospital for dehydration. She adds that her daughter has been somewhat of a "sickly" child throughout her life and has difficulty gaining weight. She has suffered from recurrent respiratory "viral" illnesses and bouts of abdominal pain. In recent years this has led to excessive absenteeism from school. This prompted consultation with a pediatric gastroenterologist about 1.5 years ago. The patient was diagnosed with celiac disease following endoscopy and biopsy.

Diagnostic findings, Part 1

On physical examination the patient's blood pressure is 90/58 mm of Hg, the temperature is 97.4 °F, heart rate is 138 beats per min, respiratory rate is 20 breaths per minute, and oxygen saturation at room air is 99%. Her weight is 57 lb. She appears thin and frail. The mucous membranes are dry. The patient's skin has a somewhat tan to bronze coloring, especially in the sun-exposed areas. The hyperpigmentation is prominent over elbows, knees, and knuckles.

Abdominal examination reveals a soft abdomen with hypoactive bowel sounds and mild tenderness across the lower abdominal quadrants without guarding. No other positive findings are present.

Questions/discussion points, Part 1

What is the differential diagnosis for this patient presenting with acute abdominal pain, fatigue, weakness?

The differential diagnosis of a patient presenting with fatigue and weakness, and acute abdominal pain includes a wide array of etiologies

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including infectious and inflammatory causes, endocrine disorders, toxic exposures, biliary and renal disease, and gastrointestinal abnormalities.[2] A thorough patient history, physical examination, and appropriate laboratory tests are essential to establish the diagnosis.

Common infectious causes of abdominal pain include viral and bacterial gastrointestinal infections. Abdominal pain can be accompanied by vomiting and, typically, diarrhea. Frequently encountered infections include bacteria (*Escherichia coli, Campylobacter jejuni, Salmonella* spp, *Shigella* spp), viruses (norovirus and rotavirus), and parasites (giardiasis, cryptosporidium, amebiasis).[3] Bacterial pathogens, although less common, often induce more severe pain. Invasive pathogens may cause bloody enteritis.

Disorders leading to intra-abdominal inflammation often cause pain that diffuses initially, becoming more localized as and when the peritoneum is involved. Some examples of inflammatory pain are appendicitis, pancreatitis, cholecystitis, inflammatory bowel disease (Crohn disease and ulcerative colitis), diverticulitis, and pelvic inflammatory disease. As the disease progresses, the patient may develop rigidity or involuntary guarding. Advanced inflammation may lead to perforation in some cases. This causes abrupt pain that is severe and presents with generalized guarding and rigidity when significant intra-abdominal free air or fluid is present. Examples of diagnoses that can be complicated by perforation include peptic ulcer, inflammatory bowel disease, diverticulitis, and appendicitis.[4] Pain secondary to obstructive pain is colicky with spasms of increased intensity. Colicky pain is seen in intestinal obstruction, intussusception, biliary colic, and ureteric colic.[4]

Metabolic or endocrine causes of abdominal pain may produce an acute abdomen that resembles pain due to an inflammatory process. These include causes, such as diabetic ketoacidosis, hypercalcemia, adrenal insufficiency, and acute intermittent porphyria.[4]

Several other conditions may produce "pain out of proportion to the physical findings" and include pancreatitis and vascular disorders (abdominal aortic aneurysm, mesenteric ischemia, ovarian torsion, and splenic vein thrombosis).[4]

Diagnostic findings, Part 2

Given her generalized abdominal pain, anorexia, fever, and vomiting with dry heaves, the initial differential diagnoses included appendicitis, inflammatory bowel disease, and viral/bacterial gastroenteritis. Laboratory investigations are ordered and include a complete blood count, comprehensive metabolic panel, lipase, and urinalysis. The results are detailed in Tables 1 and 2.

Table 1
Initial laboratory investigations for the patient.

Component	Patient's results	Standard range
Complete blood count (CBC)		
White blood cell (WBC) count (x10^6/μL)	9.7	5.0–14.5
Red blood cell (RBC) count (x10^6/μL)	5.28	3.9–5.3
Hemoglobin (g/dL)	15.2	11.5–14.5
Hematocrit (PCV) (%)	43.4	34.0–40.0
Mean corpuscular volume (MCV) (fL)	82.2	76.0–90.0
Mean corpuscular hemoglobin (MCH) (pg)	28.8	25.0–31.0
Mean corpuscular hemoglobin concentration (MCHC) (g/dL)	35	32.0–36.0
RBC distribution width (RDW-CV) (%)	12.8	11.5–14.0
Platelet count (/μL)	373,000	150,000–450,000
Reticulocyte count (%)	2	0.5% to 2.5%
Peripheral smear confirmed normocytic normochromic picture. The differential leukocyte count is normal except for the eosinophil count of 10%.		
Comprehensive metabolic profile (CMP)		
Glucose, serum (mg/dL)	60	70–110
Blood urea nitrogen (BUN), serum (mg/dL)	19	5–25
Creatinine, serum (mg/dL)	0.6	0.12–1.06
BUN–creatinine ratio	30	6–20
eGlomerular filtration rate (mL/min/1.73 m^2)	102	> 59
Sodium, serum (mmol/L)	127	135–145
Potassium, serum (mmol/L)	5.0	3.5–5.2
Chloride, serum (mmol/L)	102	95–105
Calcium, serum (mg/dL)	10.2	8.7–9.8
Bicarbonate, blood (mmol/L)	15	23–29
pH (Blood)	7.2	7.35–7.45
Anion gap (mmol/L)	10	3–11
Protein, total, serum (g/dL)	8.1	6–8
Albumin, serum (g/dL)	4.2	3.7–5.5
Globulin, serum (g/dL)	3.9	2–3.5
A–G ratio	1.1	1.1–2.5
Aspartate aminotransferase, serum (AST) (IU/L)	37	0–40
Alanine aminotransferase, serum (ALT) (IU/L)	41	6–45
Bilirubin, total, serum (mg/dL)	0.8	0.2–1.0
Alkaline phosphatase, serum (IU/L)	328	145–320
Additional lab studies		
C-Reactive protein (CRP) (Non-cardiac) (mg/dL)	< 0.29	0.00–0.75
Lipase U/L	24	10–140
Osmolality, serum (mOsm/kg)	259	274–295

Questions/discussion points, Part 2

Discuss the laboratory findings and the differential diagnosis based on the investigations

The laboratory investigations are not consistent with an infectious or inflammatory process. The total leukocyte count is normal along with no evidence of neutrophilia or left shift and no increase in reactive lymphocytes. In addition, the normal CRP level is inconsistent with an inflammatory process. The patient's presenting features of abdominal pain, fatigue, and electrolyte imbalance, at first glance, could be secondary to a viral infection and dehydration. However, the laboratory findings rule these out.

That said, laboratory findings are not normal. The most striking abnormalities include a low bicarbonate level of 15 mmol/L with a normal anion gap. This indicates a non-anion gap metabolic acidosis. In addition, hyponatremia is present with a low sodium level of 127 mmol/L.

Hyponatremia can be seen due to several pathologies and the first step in differentiating the cause of hyponatremia would be to rule out causes of false or normal osmolality hyponatremia and high osmolality hyponatremia.[2] Normal protein concentration helps rule out normal osmolality hyponatremia, which is most commonly, caused by hyperproteinemia or occasionally hyperlipidemia. High osmolality conditions, such as diabetic ketoacidosis or hyperglycemia can also cause hyponatremia and can be ruled out based on the low glucose level and low serum osmolality. SIADH is another condition that may cause hyponatremia but

Table 2
Urinalysis results of the patient.

Test	Patient's findings
Urine dipstick test findings	
Specific gravity	1.023
pH	5.0
Leukocytes	Negative
Blood/hemoglobin	Positive
Nitrites	Negative
Ketones	Negative
Bilirubin	Negative
Urobilinogen	Normal
Proteins	Negative
Glucose	Negative
Urine microscopy	
RBCs	2/hpf
WBCs/Pus Cells	3/hpf
Casts	Not seen
Crystals	Not seen
Epithelial cells	1/hpf

is ruled out due to polyuria. Other possible endocrine disorders causing hyponatremia that should be considered are adrenal insufficiency and hypothyroidism.

How would you refine the provisional diagnosis considering the clinical features along with lab investigations?

The presenting clinical features of general weakness, fatigue, malaise, poor weight gain, dehydration, abdominal pain, and skin pigmentation combined with diagnostic findings of hypoglycemia, hyponatremia, non-anion gap metabolic acidosis in the presence of normal renal and hepatic function are highly indicative of an adrenal dysfunction.[2,5] Weight loss is unlikely in hypothyroidism. Adrenal insufficiency can cause severe hypoglycemia in children and hypotension is seen in nearly all patients. General weakness, fatigue, malaise, anorexia, and weight loss are invariable accompanying features.[2,5,6] The presence of gastrointestinal symptoms, such as nausea, vomiting, and abdominal pain may be confusing and could lead to an erroneous diagnosis of an intra-abdominal pathology, for example, appendicitis. The endocrine-related acute abdomen is seen especially in patients in whom acute adrenal crisis is superimposed on chronic adrenal insufficiency. The acute adrenal crisis may be precipitated by the presence of an acute infection or stress.[5,6]

What is the mechanism for hyponatremia and metabolic acidosis in adrenocortical insufficiency?

Hyponatremia in adrenocortical insufficiency is a result of deficiency of both aldosterone and cortisol. Aldosterone binds to the mineralocorticoid receptors on the epithelial cells of the renal collecting ducts, thereby regulating sodium concentration by activating sodium channels. Lack of aldosterone thus causes decreased sodium reabsorption in the collecting ducts, leading to hyponatremia due to sodium wasting. Although the specific mechanism of sodium concentration by cortisol is not well understood, it is suggested cortisol insufficiency induces ADH secretion, resulting in a SIADH-like condition. Lack of cortisol leads to the secretion of antidiuretic hormone (ADH), causing further worsening of the hyponatremia.[7]

Metabolic acidosis in adrenocortical insufficiency is mainly due to the insufficiency of aldosterone. This results in decreased acid secretion in the kidney causing renal tubular acidosis (type 4 non-anion gap). The deficiency of aldosterone decreases the reabsorption of bicarbonate in the tubules. The main defect is at the cortical collecting duct, where acidification of urine and potassium secretion occur.[2,6,7] Aldosterone insufficiency decreases potassium secretion in the collecting tubule, which can lead to hyperkalemia. Hyperkalemia inhibits ammonia production in the proximal convoluted tubule, which decreases urinary ammonium excretion. Ammonium serves as another means of acid secretion.[8]

What diagnostic and laboratory tests should be performed to confirm the provisional diagnosis?

The low blood glucose level, dehydration, and random plasma cortisol level, along with normal renal and hepatic function, are highly indicative of adrenal dysfunction. To confirm the provisional diagnosis of adrenal insufficiency, random plasma cortisol, and adrenocorticotrophic hormone assay should be done.

Diagnostic findings, Part 3

A provisional diagnosis of adrenal insufficiency and possibly adrenal crisis (in the light of the recent upper respiratory tract infection) should be considered at this stage.

Further tests to confirm the provisional diagnosis of adrenal insufficiency are ordered and are listed in Table 3.

Table 3
Laboratory tests to confirm the provisional diagnosis of adrenal insufficiency.

Component	Patient's results	Standard range
Random plasma cortisol (μg/dL)	2.0	> 18
Adrenocorticotrophic hormone (ACTH) ng/L	1992	0–47
Thyroid-stimulating hormone (TSH) (mIU/L)	1.11	0.5 to 5.0
Thyroxine hormone (Free T4) (ng/dL)	1.0	0.8 to 1.8
Anti-peroxidase antibodies	Absent	

Questions/discussion points, Part 3

What is the rationale for testing thyroid function and/or hormones in suspected adrenal insufficiency?

Normally there is no requirement for testing thyroid functions in a patient with features of adrenal insufficiency. However, the patient's presentation describes that she was previously diagnosed with celiac disease. The presence of celiac disease in this patient suggests an autoimmune pathology that may affect multiple endocrine glands or may be a part of an autoimmune polyglandular syndrome (APS).[9,10] There may be associated autoimmune thyroiditis and hypothyroidism, especially in APS-2.[11] Additionally, increased TSH may occur in patients with autoimmune primary adrenocortical insufficiency (Addison disease) as the autoimmune pathology may affect multiple endocrine organs. TSH may be increased alone or seen along with low thyroxine and/or detectable thyroid autoantibodies. Symptoms and signs of hypothyroidism may not be present. TSH and other clinical features of hypothyroidism, if apparent, may reverse with glucocorticoid replacement.[12] In the setting where both disorders are present and laboratory investigation results suggest that treatment is required, corticosteroids should be given before thyroid hormone replacement to avoid precipitating an acute adrenal crisis.

What is the interpretation of the lab investigations seen in Table 3?

The patient's random plasma cortisol is significantly reduced, suggesting an adrenal insufficiency. Adrenal insufficiency could be primary or secondary and would need to be differentiated after the adrenal insufficiency is confirmed (Fig. 1). The point to remember is that a random plasma cortisol level can be normal in early adrenal insufficiency. Therefore, random plasma cortisol levels normally have little utility in the "diagnosis" of adrenal insufficiency. That said, a plasma cortisol > 18 μg/dL, either at baseline or at 30 min when doing a stimulation test (see next question), effectively rules out a diagnosis of primary or secondary adrenal insufficiency. In a patient with clinical signs and symptoms of insufficiency, random plasma cortisol is typically decreased in both primary and secondary adrenal insufficiency. Plasma ACTH levels are high in primary adrenal insufficiency and absent or low in secondary adrenal insufficiency (Figs. 1 and 2). The patient's ACTH levels are significantly high, suggesting a primary adrenal insufficiency. At this point, the morning plasma cortisol and ACTH results can be used as diagnostic tests when confirmatory tests are not possible.[13]

The thyroid function tests are normal and rule out thyroid pathology, including autoimmune thyroiditis.

Discuss the confirmatory tests for the diagnosis of adrenal insufficiency and how they help differentiate between primary and secondary adrenocortical insufficiency

ACTH (Cosyntropin) stimulation test, is considered the "gold standard" for confirming the diagnosis of adrenal insufficiency.[13] The test is done by parenteral (intramuscular or intravenous) administration of 250 μg of cosyntropin after obtaining a blood sample for basal plasma cortisol level. Following cosyntropin stimulation, blood samples are collected at

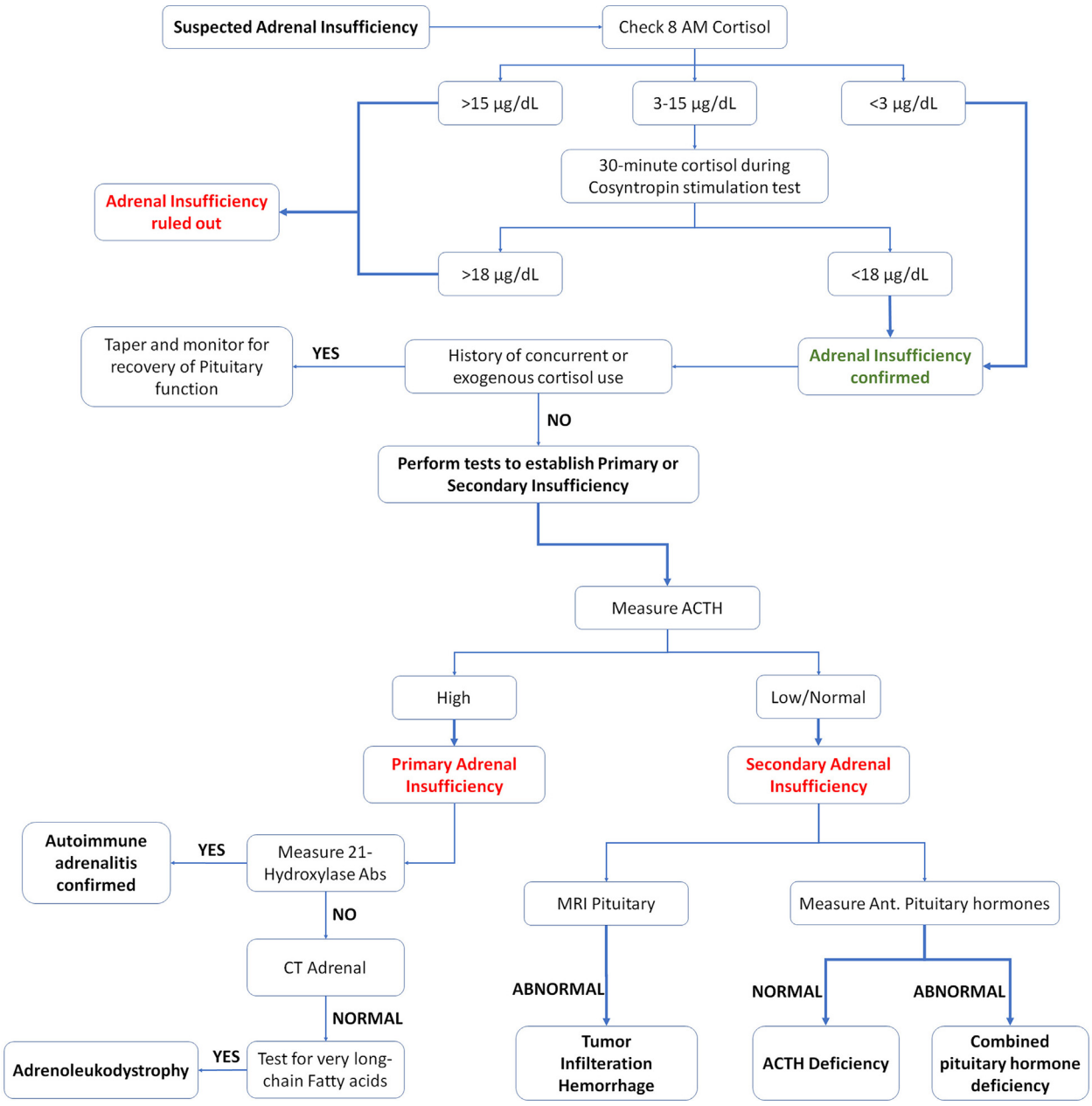

Fig. 1. Schema for investigation of suspected adrenal insufficiency to confirm the diagnosis of adrenal insufficiency.

30 min and 60 min. Post-cosyntropin stimulation, a cortisol value increase of < 7 µg/dL over the basal level or a value of < 18 µg/dL at 60 min confirms the diagnosis of primary adrenal insufficiency (Fig. 1).

If a diagnosis of primary adrenal insufficiency is confirmed, an assay for adrenal autoantibodies should be obtained (Fig. 1). Additionally, these patients should be screened for other autoimmune diseases such as hypo- or hyperthyroidism, pernicious anemia, or type 1 diabetes mellitus.[6] If no adrenal antibodies are detected, other causes including infectious, hemorrhagic, and neoplastic etiologies, should be investigated and imaging studies (e.g., abdominal or cranial CT or MRI) should be performed (Fig. 1). Calcifications are present with certain infectious causes, for example, tuberculosis and can be detected with plain X-ray or ultrasound scan.[5,6,14] A rare cause of adrenal insufficiency is adrenal metastases.[14] Human immunodeficiency virus (HIV) detection test could be performed where indicated.[13]

Secondary adrenal insufficiency should be considered if the morning plasma basal cortisol value is < 5 µg/dL, suggesting adrenal insufficiency; morning plasma ACTH is < 5 pg/mL, and post-cosyntropin stimulation test shows an increase in cortisol levels to within normal or subnormal range (Fig. 1). A prolonged (24 h) post-cosyntropin test should reveal a continued rise in cortisol levels for 24 h.[5,6]

If secondary adrenal insufficiency is confirmed, a CT or MRI of the brain should be done to determine the cause (e.g., pituitary tumor or pituitary atrophy).[6] To differentiate adrenal insufficiency due to pituitary or hypothalamic pathology, the corticotropin-releasing hormone (CRH) test can be done. However, this is rarely used in clinical practice. The test is done by administration of CRH 100 µg (or 1 µg/kg) intravenously. A rise of plasma ACTH of 30–40 pg/mL (6.6–8.8 pmol/L) is considered a normal response. No response would be seen in patients with pituitary failure, whereas those with hypothalamic disease will record an increase in ACTH due to a functioning and responsive pituitary.[5]

Diagnostic findings, Part 4

Further tests to confirm the diagnosis and differentiate between primary and secondary adrenal insufficiency are ordered. ACTH

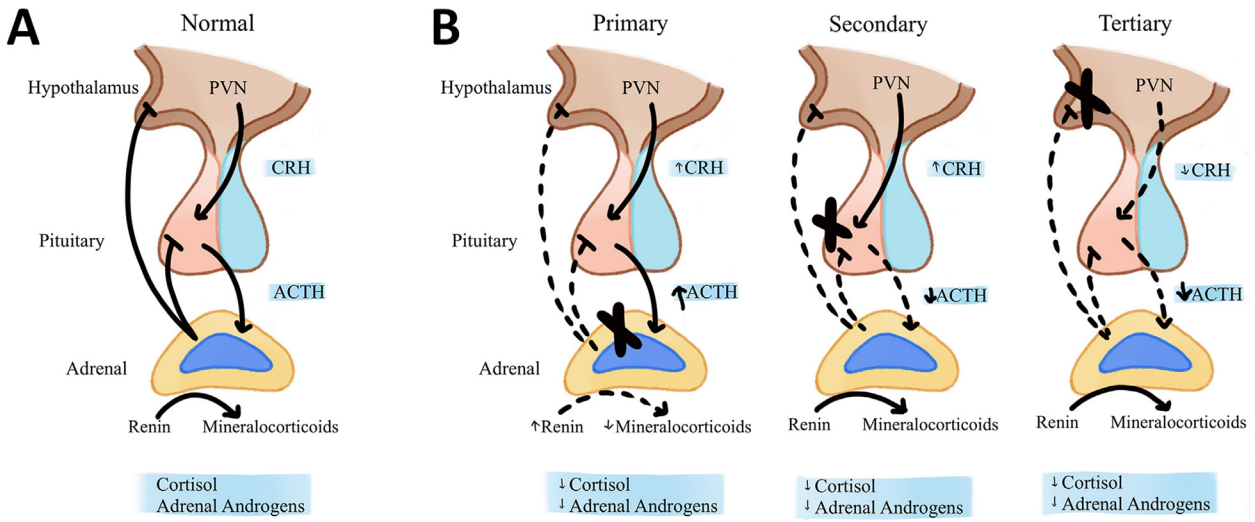

Fig. 2. The part of the hypothalamic-pituitary-adrenal axis affected determines the type of adrenal insufficiency. (A) Demonstrates the normal hypothalamus–pituitary–adrenal axis. (B) In primary adrenal insufficiency, the adrenal cortex is destroyed that causes loss of both glucocorticoid and mineralocorticoid activity. This causes high levels of renin in the blood. In contrast, secondary adrenal insufficiency reflects an inability of the hypothalamic-pituitary axis to deliver ACTH, thus reducing trophic support to a normal adrenal gland. This results in a decrease of only cortisol production, as mineralocorticoid production is mostly independent of ACTH and mainly regulated by renin. The hypothalamic disease presents similar to pituitary disorders, where CRH is deficient leading to reduced ACTH and cortisol. This is sometimes termed tertiary adrenal insufficiency. (Figure illustration by the artist Mikayla Bierschbach and included with her permission).

(Cosyntropin) stimulation test, considered the "gold standard," is done to confirm the primary adrenal insufficiency.

Prior to administration of exogenous ACTH, the base cortisol value was 2.5 μg/dL. Plasma cortisol values at 30- and 60-min post-ACTH administration are recorded as 1.7 μg/dL and 2.1 μg/dL, respectively. This confirms a diagnosis of primary adrenal insufficiency and is followed by the anti-21 hydroxylase antibody test, which is positive and confirms an autoimmune adrenalitis.

The results strongly suggest primary adrenal pathology. Secondary adrenal insufficiency is unlikely. However, in the absence of hyperkalemia, it is uncertain if mineralocorticoid function is also abrogated.

Questions/discussion points, Part 4

How is the mineralocorticoid deficiency assessed in a patient with adrenocortical insufficiency?

To assess potential mineralocorticoid deficiency, plasma renin and aldosterone should also be assessed. They are both early indicators of primary adrenal insufficiency (Fig. 2). Hyponatremia alone does not indicate a mineralocorticoid deficiency as it can occur with isolated cortisol deficiency as well.[2] Hyperkalemia due to low aldosterone levels is another indicator of mineralocorticoid deficiency. However, hyperkalemia may not be present in all patients. The presence of attendant mineralocorticoid deficiency causes high levels of plasma renin, and aldosterone will be either low or at the lower range of normal value. A look at normal adrenal functional histology can explain this further. There are three distinct zones in the adrenal cortex. The outermost zone is the zona glomerulosa that synthesizes aldosterone and is predominantly regulated by the renin-angiotensin axis along with concentrations of extracellular potassium. As the regulation of aldosterone is not controlled by the pituitary, it explains why the aldosterone synthesis and secretion are not abrogated in secondary (loss of ACTH) and tertiary (loss of CRH) adrenocortical insufficiency. ACTH in response to CRH primarily regulates the secretion of cortisol by the zona fasciculata. Thus, the observed biochemical and clinical progression suggests that the autoimmune damage affects the zona glomerulosa first and the zona fasciculata is damaged later. Zona fasciculata is perhaps protected by local release of glucocorticoids or due to its thickness (bulk).[15] Zona reticularis, the innermost layer of the adrenal cortex synthesizes and secretes the adrenal androgens and may also be destroyed late in the disease. Attendant adrenal androgen deficiency, in women, can be assessed with androstenedione and dehydroepiandrosterone (DHEA) levels.[6] This is not possible in men, as testes are the primary source of androgens.

What are the various differentiating features and causes of primary and secondary adrenocortical insufficiency? Discuss pathology and pathogenesis in the context of the hypothalamic-pituitary-adrenal (HPA) axis

Adrenocortical insufficiency, a potentially life-threatening disorder is characterized by the decreased production or action of glucocorticoids and/or mineralocorticoids and sometimes may also have a loss of adrenal androgens. It is classified as either primary (adrenal cortical pathology) or secondary (anterior pituitary or hypothalamic pathology) depending on which component of the hypothalamic-pituitary-adrenal (HPA) axis is impacted (Fig. 2). Clinical features are precipitated due to the insufficient secretion of cortisol and/or aldosterone from the adrenal cortex. It is important to differentiate whether the insufficiency is primary or secondary. This is because the etiology, immediate treatment, and long-term management, differ depending on the causes of adrenal insufficiency.

Primary adrenal insufficiency results from adrenal gland malfunction and its clinical manifestations are due to deficiencies in cortisol and aldosterone (Fig. 2). Androgen deficiency may also be present, as steroidogenesis is affected by adrenal cortex malfunction.

Primary adrenal insufficiency was first described by Thomas Addison in 1855.[16] Also called Addison disease, it is defined as the clinical manifestation of sustained glucocorticoid and/or mineralocorticoid deficiency due to failure of the adrenal cortex. The various causes that lead to abrogation of the adrenal cortex are as follows:

A. *Autoimmune adrenalitis* is the most common cause of primary adrenocortical insufficiency.[17] It comprises over 80–90% of primary adrenal insufficiency cases. About 40% of this cohort are classified as a sporadic disease and have isolated destruction of the adrenal cortex by an autoimmune process. The rest (60%) present with multiple endocrine involvements and are classified as autoimmune

polyendocrinopathy syndromes (APS).[6,9,11,14,17,18] Antibodies to the 21-hydroxylase enzyme are seen in patients with autoimmune adrenalitis and are an excellent marker for adrenal autoimmunity.[19] However, although 21-hydroxylase antibodies are excellent markers of adrenal autoimmunity, they do not appear to be involved in the pathogenesis of the disease; a T cell-mediated adrenal cortical destruction occurs due to $CD8^+$ cytotoxic lymphocyte infiltration and suppression of $CD4^+$ regulatory lymphocytes.[14,19] The trigger mechanism for the autoimmune process is not well understood and several factors (e.g., viral infection, stress, smoking, pollutants) have been postulated. Histopathology reveals lymphocytic infiltration of all three layers of the adrenal cortex. Plasma cells, macrophages, and fibrosis are seen. A few islands of regenerating adrenocortical cells may be present in the early stages but ultimately the entire cortex is replaced by fibrosis.[20] Immunohistochemistry confirms infiltration by activated T lymphocytes especially CD8+.[6,14,15] The adrenal medulla is spared in the autoimmune disease, unlike in the other non-autoimmune forms of AD discussed below .[2,6]

APS includes several distinct syndromes with distinct gene mutations–linkages. The pathogenic mechanisms for APS are poorly understood.

a. *APS-1 or Whitaker syndrome* is an autosomal recessive disorder with a single gene mutation on chromosome 21q22 (*AIRE* gene). It manifests in children and young adults and presents most often with three components: adrenalitis, hypoparathyroidism, and chronic mucocutaneous candidiasis.[21] Additional features include ectodermal dystrophy affecting nails, skin, alopecia, and dental enamel along with single or multiple autoimmune disorders, for example, pernicious anemia celiac disease, and ovarian or testicular failure, etc..[15,21] AIRE is a transcription factor that enhances the expression of peripheral tissue antigens in the thymus and is involved in the elimination of self-reactive T cell clones. *AIRE* gene mutation, therefore, compromises central T-cell tolerance and leads to autoreactive T cells that cause an autoimmune response.[22] Autoreactive antibodies against IL-17 and IL-22 are found in these individuals with a compromise of Th-17 response. Patients develop mucocutaneous candidiasis as a result of an absence of antifungal Th-17 cytokines.[14]
b. *APS-2 or Schmidt syndrome* is a polygenic disorder linked to class II HLA antigens, specifically HLA DR3/DQ2 and HLA DR4.4/DQ8 haplotype, and also a class I HLA MIC-A5.1.[9,15] APS-2 has a higher prevalence than APS-1 and manifests later in the third or fourth decade of life. Clinical features include multiple autoimmune disorders, for example, Addison disease, thyroiditis, with or without type 1 diabetes mellitus.[11] Other autoimmune diseases, for example, gastritis, vitiligo, alopecia, hepatitis, hypophysitis, celiac disease, etc., may also be associated.[18]
c. *A rare syndrome APS-4* has been described and includes autoimmune adrenalitis and other autoimmune diseases not included in APS-1 or APS-2.[14,15]

B. *Infections:* The primary adrenal insufficiency first described by Thomas Addison was due to tuberculous infection as a complication of pulmonary tuberculosis with dissemination to other organs.[16] Tuberculosis, though an important cause,[6,16] is less common now with the advent of antimycobacterial drugs and control of mycobacterial infection. Especially in the developed countries, cases may still be encountered in endemic areas, for example, lower-income nations. Fungal adrenalitis may be seen with disseminated opportunistic infections (e.g., *Histoplasma capsulatum, Coccidioides immitis,* and others).[17,23] HIV/AIDS patients also have a high risk for developing adrenal infections from cytomegalovirus (CMV), *Mycobacterium avium-intracellulare,* and complications of HHV-8 infection such as Kaposi sarcoma.[24] Other rare causes include intra-adrenal hemorrhage[25] and Waterhouse–Friderichsen syndrome following meningococcal sepsis and other gram-negative bacterial septicemia[26]; amyloidosis; hemochromatosis, etc.

C. *Metastatic and primary neoplasms:* Partial chronic adrenal insufficiency may be produced due to metastatic destruction of a part of the adrenal gland. The most common tumors that metastasize to adrenals are lung and breast; in addition, gastrointestinal adenocarcinomas, malignant melanoma, and some hematopoietic neoplasia are also reported.[27] A rare presentation includes bilateral primary lymphoma.[28]
D. *Genetic cause*: Adrenal hypoplasia congenita, a rare X-linked disease due to mutation of *NROB1* gene is characterized by hypoplasia of adrenal development due to the missing DAX1 transcription factor.[29] To establish the stem/progenitor cell niche of the definitive cortex from the adrenal primordia DAX1 needs to promote regression of the fetal zone so that the adrenal cortex can develop. The absence of DAX1 prevents this process leading to hypoplastic development of the adrenal cortex.[30] Adrenoleukodystrophy is the other X-linked genetic cause of adrenal insufficiency due to mutation of the *ABCD1* gene. The disorder is characterized by a defect in the breakdown of long-chain fatty acids. It affects steroidogenesis in the adrenal gland leading to adrenal insufficiency.[31]
E. *Congenital adrenal hyperplasia* is an extremely rare cause of adrenocortical insufficiency. Adrenal insufficiency is a result of enzyme defects causing a block in the production of corticosteroids and/or mineralocorticoids in the adrenal cortical cells. ACTH-induced cortical hyperplasia due to this non-function is the hallmark of this condition.[32]
F. *Drug-induced or iatrogenic* causes include surgical removal of adrenal glands and drugs, such as metpyrone, antifungals (e.g., ketoconazole), and the sedative agent etomidate can also cause abrogation of the function of the adrenal cortical cells or ACTH secretion leading to the features of adrenal cortical insufficiency.[6]

Secondary adrenal insufficiency is due to a lack of ACTH. Importantly, in contrast to primary adrenal insufficiency, aldosterone secretion is preserved in secondary and tertiary adrenal insufficiency. The independent loop of stimulation of aldosterone through the renin-angiotensin-aldosterone pathway is preserved, thereby allowing adrenal stimulation via this secondary mechanism (Fig. 2). Due to this preservation, hyperkalemia and metabolic acidosis due to aldosterone insufficiency are not a feature of secondary adrenal insufficiency.[6]

Secondary adrenal insufficiency is most often caused by either pituitary or hypothalamic tumor that leads to loss of function, that is, hypopituitarism.[6,14,17] Tumors of the pituitary are space-occupying lesions that crowd out the normal cells of the pituitary leading to a lack of ACTH production and secondary adrenal insufficiency. Due to the lack of required ACTH mediated stimulation, the normal adrenal gland fails to produce and secrete cortisol.[6,14,17] Iatrogenic loss of function of the pituitary or hypothalamus may result from radiotherapy or surgical removal of tumors in the area.[6,14,17] Hypothalamic pathology causes abrogation of corticotrophin-releasing hormone (CRH) production and thereby lack of ACTH production by pituitary.[6]

Another important cause of secondary insufficiency is an inappropriate withdrawal of chronic high dose corticosteroid or glucocorticoid therapy. In this scenario, the high-dose cortisol therapy suppresses the ACTH production by the negative feedback to the pituitary leading to suppression and/or atrophy of ACTH secreting cells and adrenal cortex. A sudden cessation of therapy leads to a lack of cortisol, but the pituitary response is not immediate, thereby precipitating adrenal insufficiency.[2] Rare causes of secondary adrenal insufficiency include pituitary hemorrhage, pituitary apoplexy due to tumor infarction, or Sheehan syndrome.[6,33]

Diagnostic findings, Part 5

Plasma renin and aldosterone levels were determined and are listed in Table 4. High renin and low aldosterone levels support the loss of mineralocorticoid activity and therefore, strengthen the diagnosis of primary autoimmune destruction of adrenal gland cortex in addition to the high ACTH levels[6] and the lack of increase in plasma cortisol levels post-cosyntropin stimulation test.

Table 4
Laboratory investigations to confirm mineralocorticoid deficiency.

Component	Patient's results	Standard range
Aldosterone (lying down) (ng/dL)	1.2	3–35
Renin (ng/mL/hour) on a normal sodium diet	6.7	0.6–4.3

A final diagnosis of acute presentation of primary adrenal insufficiency due to autoimmune adrenalitis with coexisting celiac disease (in remission) is made. The presence of anion gap metabolic acidosis suggests decompensation and precipitation of adrenal crisis. The presence of a respiratory tract infection for four days appears to be the reason for the acute decompensation and precipitation of adrenal crisis.

Questions/discussion points, Part 5

Compare and contrast how acute and chronic adrenal insufficiency correlate with clinical features, pathology, and laboratory findings

The characteristic and most dramatic clinical presentation of acute adrenal insufficiency or "adrenal crisis," due to either primary or secondary pathology is hypotension or shock, but patients may have additional findings such as anorexia, nausea, vomiting, abdominal pain, weakness, fatigue, lethargy, confusion, and even coma. These clinical manifestations primarily result from acute loss of glucocorticoid and mineralocorticoid effects. Adrenal crisis may also be precipitated due to a stressor, for example, infection or anesthesia,[34,35] in patients with underlying chronic adrenal insufficiency. Another cause for sudden adrenal insufficiency presenting as the adrenal crisis may be seen in patients on long-term high dose corticosteroid therapy for immunosuppression (e.g., rheumatoid arthritis, systemic lupus erythematosus, etc.) if there is sudden withdrawal or stoppage of therapy.

Acute adrenal insufficiency is most likely to be caused by bilateral adrenal hemorrhage, metastasis, or an acute infection that causes severe damage to the adrenal cortex. Adrenal hemorrhage can have several etiologies. These may include coagulopathies, heparin-induced thrombocytopenia, primary anti-phospholipid syndrome, and meningococcal (*Neisseria meningitidis*) sepsis known as Waterhouse–Friderichsen syndrome. Other less common causes of Waterhouse–Friderichsen syndrome include hemorrhagic complications of septicemia due to Gram-negative bacteria (*Pseudomonas* species, pneumococci, and *Haemophilus influenzae)* causing disseminated intravascular coagulation.[26] Acute adrenal insufficiency may also be precipitated due to hypoxia (mainly seen in newborns), complications of anticoagulant therapy,[25] and secondary causes such as gestational apoplexy or Sheehan syndrome.[33]

Chronic adrenal insufficiency, in contrast, develops gradually with adrenocortical destruction due to autoimmune, tuberculous, or other infiltrative diseases. The symptoms and signs typically develop over months and years. This results in a more protracted syndrome of malaise, fatigue, anorexia, weight loss, joint pain, back pain. Patients may crave salt due to chronic hyponatremia. Hyperpigmentation of the skin is a specific feature of chronic disease. Darkening of the skin especially in the creases of the hands, extensor surfaces, recent scars, buccal and vaginal mucosa, and nipples may be seen. Hyperpigmentation is a result of alpha-melanocyte-stimulating hormone (MSH) excess, a hormone transcribed along with ACTH.[36] Both MSH and ACTH are produced from the precursor proopiomelanocortin (POMC) in the secretory vesicles of the pituitary. MSH originating from the pituitary affects skin pigmentation in humans.

In the initial stages of the chronic disease with primary pathology, the ACTH stimulation test may be normal. As the disease progresses, high plasma renin levels may be seen first followed by low aldosterone, normal basal cortisol, and normal ACTH levels.[15] While basal glucocorticoid secretion is maintained at normal levels, the required response of upregulation during stressors, such as surgery, trauma, or infection is absent; these stressors cause a higher requirement and therefore, may result in the precipitation of acute adrenal crisis or insufficiency.[34,35,37] As the disease progresses a slow and continued destruction of the adrenal gland occurs resulting in decreased adrenal glucocorticoid reserve within the gland and raised ACTH levels, followed by low basal levels of cortisol.[15] As the loss of cortical tissue progresses, there is continued reduction of even basal secretion of glucocorticoids and mineralocorticoids. Ultimately the gradual destruction leads to the development of worsening clinical manifestations.[15,17,23] The fall in plasma cortisol reduces the feedback inhibition of the pituitary stimulating ACTH secretion leading to a rise in plasma ACTH levels. The renin levels are very high with markedly low cortisol and aldosterone levels.[15,17,23] The loss of adequate levels of glucocorticoid and mineralocorticoids precipitates hyponatremia. Hyperkalemia may also be seen in some patients.

Hyponatremia, seen in chronic (both primary and secondary) adrenal insufficiency, may induce "salt craving" and unusual food preferences for high salt foods, for example, the brine from pickles. Associated biochemical features for both acute and chronic presentations include hyponatremia, hypoglycemia, hyperkalemia, unexplained eosinophilia, and mild pre-renal azotemia due to dehydration and accompanying hypovolemia.[15,18,19,23] Increased stress (e.g., infection or trauma) in chronic adrenal insufficiency patients may require higher amounts of glucocorticoid and mineralocorticoid supplementation and can precipitate acute adrenal insufficiency.[35]

What are the clinical features of adrenocortical insufficiency in older adults?

In older adults, the adrenocortical insufficiency may be missed as it may have an insidious onset. The presenting features may be non-specific tiredness, drowsiness, and delirium. They may have falls due to dizziness, resort to immobility and physical examination will elicit orthostatic hypotension. There is an increased risk of adrenal crisis in older adults that are on physiological glucocorticoid replacement therapy and may be a result of poor adherence to or withdrawal of therapy and a higher chance of intercurrent illnesses that need a higher dose adjustment. It is therefore very essential to educate both patient and carer to seek help as soon as an intercurrent illness develops or in the situation of increased stress.[6]

What is the treatment for adrenocortical insufficiency? Discuss in the context of precipitating events or basic pathology

Initial treatment for adrenal crisis involves correction of life-threatening hemodynamic and metabolic derangements resulting from cortisol deficiency. Blood sugar should be rapidly assessed, and hypoglycemia should be treated with intravenous dextrose. Hypovolemic shock is initially resuscitated with intravenous normal saline followed by vasopressors. However, these measures alone are unlikely to be successful. Definitive treatment involves administration of exogenous glucocorticoid, typically in the form of intravenous hydrocortisone or dexamethasone.[38] In unstable patients, treatment should be immediately started and not be delayed pending confirmation of diagnosis.

Patients with chronic adrenal insufficiency require long-term maintenance with both glucocorticoid and mineralocorticoid therapy. Hydrocortisone and fludrocortisone are typically prescribed. During periods of illness or physiologic stress, an increased hydrocortisone dose is typically provided to avoid precipitation of adrenal crisis.[38]

Teaching points

- Unexplained hypotension, fatigue, and hyponatremia with or without hyperkalemia should raise suspicion for adrenal insufficiency.
- Laboratory findings include hyponatremia, hypoglycemia, hyperkalemia, unexplained eosinophilia, along with mild pre-renal azotemia.

- Primary adrenal insufficiency is distinguished by elevated plasma ACTH levels and elevated renin values with or without hyperkalemia. Secondary adrenal insufficiency, however, is identified by a suppressed or inappropriately normal ACTH level.
- Autoimmune destruction of the adrenal cortex is the most common cause of primary adrenal insufficiency in the US and other industrialized nations. The disorder may occur alone especially in adults or in association with autoimmune polyglandular syndromes where they may also present in childhood.
- Mineralocorticoid deficiency may be present in early primary adrenal insufficiency along with high levels of renin.
- The most common cause of secondary adrenal insufficiency is suppression of the hypothalamic-pituitary-adrenal axis by exogenous glucocorticoid administration or tumors and other lesions of the hypothalamus or pituitary gland that interfere with ACTH or CRH production, transport, or function.
- Secondary adrenal insufficiency has clinical features similar to chronic primary adrenal insufficiency, but without hyperpigmentation or mineralocorticoid abnormalities.
- The presentation of acute primary adrenal insufficiency may include hypotension, circulatory collapse, confusion, abdominal pain, and fever.
- The features of chronic primary adrenal insufficiency will have a more protracted history of malaise, salt craving, fatigue, joint and back pain, and hyperpigmentation.
- Initial treatment is focused on correction of shock and metabolic derangements, through administration of intravenous fluids, dextrose, and glucocorticoids. In patients presenting with shock and suspected adrenal crisis, therapy should be instituted prior to confirmation of the diagnosis.
- Treatment of chronic adrenal insufficiency includes administration of hydrocortisone and fludrocortisone. Increase dose of hydrocortisone should be administered during illness or periods of physiologic stress.

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