Adrenal Gland Disorders: Cushing’s Syndrome, Conn’s Syndrome, Addison’s Disease, and Phaeochromocytoma

The adrenal glands are paired endocrine organs that produce hormones secondary to neuronal influence. The glands are organized into an inner adrenal medulla that secretes Adrenaline and Noradrenaline and an outer cortex consisting of three anatomically and functionally different layers producing mineralocorticoids (aldosterone), glucocorticoids (cortisol) and androgens (androstenedione). The gland may suffer disorders of hyperfunction such as hypercortisolism, pheochromocytoma, and hyperaldosteronism or disorders of insufficiency such as Addison’s disease. This article will provide outlines for each disease separately.

Synopsis: The Adrenal Glands

The adrenal glands are a pair of key organs responsible for maintaining homeostasis in several key hormonal cycles. The adrenal medulla corresponds to a peripheral sympathetic ganglion and is responsible for the production of adrenaline and noradrenaline. The adrenal cortex consists of 3 anatomically and functionally different layers and is responsible for producing mineralocorticoids (aldosterone),
The synthesis and secretion of these various hormones are performed by a complex system of different enzyme cascades and functional circuits. The renin-angiotensin-aldosterone system (RAAS) and the neuronal control centers (hypothalamus and pituitary gland) are 2 of these circuits. It is easy to imagine that disorders in these finely-tuned systems could induce a variety of illnesses.

Hypercortisolism (Cushing’s Syndrome)

Cortisol compounds are widely used medications in modern medicine. Many people are prescribed these medications long-term. It is thus easy to infer that hypercortisolism is a relatively common disease.
**Etiology of hypercortisolism**

In the etiology, we differentiate between exogenous hypercortisolism stemming from long-term treatment with glucocorticosteroids, and an endogenous increased production and secretion of cortisol or adrenocorticotropic hormone (ACTH). Yet in all cases, the result is hypercortisolism with subsequent Cushing’s syndrome. Exogenous hypercortisolism is the most frequent cause. With the endogenous Cushing’s syndrome, one must differentiate between the ACTH-dependent and the ACTH-independent forms of the condition.

If an ACTH-producing adenoma exists in the anterior lobe of the pituitary gland or a primary hypothalamic hyperfunction, central Cushing’s syndrome is present. This is the largest group of endogenous manifestations of Cushing’s syndrome.

- The ACTH may also be increased ectopically, paraneoplastically via small cell pulmonary carcinoma, or carcinoids.
- A (reversible) increase in ACTH is also facilitated by alcohol consumption.
- ACTH-independent Cushing’s syndrome can be caused by a cortisol-producing adenoma or carcinoma of the adrenal cortex.
Symptoms of hypercortisolism

The clinical presentation of the patient stems from the manifold effects of cortisol. Impairment of lipometabolism by cortisol on the lipometabolism results in central obesity with a bull neck and moon face due to fat redistribution. The skin exhibits poor wound healing with a tendency for acne, stretch marks, atrophy, ulcers, and boils. Catabolic protein metabolism along with osteoporosis (and increased risk of fracture or osteonecrosis), myopathy, and adynamia is observed. This provokes a diabetic metabolic state. This may also cause or worsen arterial hypertension. If an ACTH-dependent form of the condition is present, androgens may also increase in number. Women experience **virilism with hirsutism and menstrual disruptions**.
Diagnosing hypercortisolism

The symptoms or medication history lead to a suspected diagnosis. Low-dosage dexamethasone inhibitor test is conducted as an initial test of effective hypercortisolism: a 2 mg dose of dexamethasone is administered in the late evening. This should actually result in suppression of endogenous cortisol production the next morning. If this does not work, hypercortisolism is present, which must then be further investigated for its etiology.

- **The corticotropin-releasing hormone (CRH) test**: ACTH concentration is measured before and after the administration of CRH. Hypothalamic hyperfunctions and pituitary adenomas (M. Cushing) undergo an increase in ACTH after CRH administration.

- **The high-dosage dexamethasone inhibitor test**: 8 mg dexamethasone is administered at midnight for 2 days. This can achieve suppression of cortisol with central Cushing’s syndrome. If an adrenal tumor or ectopic cortisol production is present, this does not work.

**Note**: Mildly abnormal screening results may represent pseudo Cushing’s syndrome (depression and alcoholism).

Imaging of the sella or adrenal glands via computed tomography (CT) or magnetic resonance tomography (MRT) is also helpful. Paraneoplastic ACTH increases sometimes entail an increase in the metabolite lipotropin.
Differential diagnosis

Along with the many causes of ‘true’ hypercortisolism, one must consider that cortisol can also be increased as a stress hormone with various psychiatric symptoms (e.g., depression). Not every adrenal tumor that happens to be discovered necessarily entails the symptoms of Cushing’s syndrome. Varieties that do not produce hormones are called incidentalomas.

Treating hypercortisolism

The treatment is oriented toward the cause of hypercortisolism. Hormonally active adrenal tumors can be easily removed with a minimally invasive laparoscopic adrenalectomy. The other side takes on the role of hormone production, although glucocorticoid substitution may be necessary for a period of time. Cushing’s syndrome secondary to a hyperfunctioning pituitary adenoma producing excess ACTH can also be treated surgically. Radiation therapy is also useful.

Note: In this case, the lifelong administration of glucocorticoids is necessary post-operatively!

Inoperable adrenal cortex carcinomas or paraneoplastic ACTH syndromes can be treated symptomatically by a blockage of cortisol production. Various compounds are available for this (ketoconazole, octreotide, metyrapone, and aminogluthethimide).

Conn’s Syndrome (Hyperaldosteronism)

Conn’s syndrome describes primary hyperaldosteronism and causes increased production of aldosterone within the adrenal cortex.
**Etiology of Conn’s syndrome**

In most cases, there is idiopathic hyperplasia of the zona glomerulosa, and this may be uni- or bilateral. More uncommonly, an aldosterone-producing adenoma may be present. This often entails a much greater number of symptoms. Causal carcinomas are rare.

**Primary and secondary hyperaldosteronism**

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<th>Primary</th>
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| The adrenal gland itself is inappropriately overproducing aldosterone without extra-adrenal cues. **Causes:**  
- Aldosterone-producing adenoma (Conn’s syndrome)  
- Bilateral adrenal hyperplasia  
- Adrenal carcinoma (rare)  
- ↑ ALDO → ↓ RENIN  
- Hypertension (HTN) – Na retention and low K+ (K+ secretion), alkalosis | The adrenal gland is acting in response to the overstimulation of the RAAS (e.g., congestive heart failure (CHF) and renal ischemia).  
- ↑ RENIN → ↑ ALDO  
  Edema, HTN, low K+, alkalosis |

**Symptoms of Conn’s syndrome**

Symptoms are usually relatively mild and accompanied by arterial hypertension and a normokalemic metabolic state. Should secondary hypertension be suspected, Conn’s syndrome should always be considered as this is responsible for about 5–10% of cases.

The distinct, but more uncommon symptoms (often coupled with the adenomas) consist of hypertension with headaches and potential organ damage, hypokalemia with muscle weakness, constipation, electrocardiogram (ECG) changes, and polyuria, as well as alkalosis.

**Diagnosing Conn’s syndrome**

The symptoms must be indicative of Conn’s syndrome. The lab chemical tests accordingly reveal increased plasma aldosterone levels with increased aldosterone/renin quotients, and possibly hypokalaemia and/or alkalosis.

**Note:** Hypernatraemia is conceivable, but is actually not present! Influential medication must be administered when determining the aldosterone/renin quotients. The administration of angiotensin-converting enzyme (ACE) inhibitors, aldosterone antagonists, or angiotensin-receptor blockers naturally alters the RAAS system. The orthostasis test can be used to differentiate between idiopathic hyperaldosteronism and an aldosterone-producing adenoma.

**Differential diagnosis**

Other causes that determine hyperaldosteronism include sodium deficiency or renal ischemia. Limited liver function or mutated renal transport channels (Bartter syndrome or Gitelman syndrome) also lead to increased secondary aldosterone levels.
Treating Conn’s syndrome

Adenomas can now be removed with a minimally invasive laparoscopic adrenalectomy. The idiopathic hyperaldosteronism is symptomatically treated with spironolactone and perhaps potassium-sparing diuretics. Carcinomas should be operatively and chemotherapeutically removed after staging. The prognosis of this condition is not good.

Adrenal Cortex Insufficiency

Insufficiency of the adrenal cortex results in the failure of hormonal regulatory circuits with the corresponding marked clinical presentation.

Etiology of adrenal cortex insufficiency

Adrenal cortex insufficiency primarily forms from a disruption in the function of the adrenal cortex. This may be localized or may be part of a generalized disease. Addison’s disease entails an autoimmune reaction with the destruction of the adrenal cortex tissue, during which the autoantibodies often target the 17 alpha-hydroxylase. One famous patient who suffered from this disease was John F. Kennedy.

Furthermore, carcinomic metastases are possible, often with pulmonary carcinomas, melanomas or kidney cell carcinomas. Infectious diseases can also damage the adrenal cortex. For instance, tuberculosis plays a significant role. Along with these rather chronic forms, acute failures of the adrenal cortex can also occur.

**Waterhouse-Friedrichsen syndrome is an expression of hemorrhagic infarction of the adrenal cortex as part of meningococcal infection.** The condition is important for its symptoms but also appears especially frequent in exams. Other causes of acute bleeding that may also damage the adrenal cortex include Marcumar therapy,
operative complications, trauma or septicemia.

The organism attempts to counteract a primary adrenal cortex insufficiency with increased ACTH levels. ACTH consists of the precursor of proopiomelanocortin, which branches off into the melanocyte-stimulating hormone (MSH) and endorphins.

Secondary damage chiefly stems from an ACTH deficiency caused by the insufficiency of the neuronal regulatory organs (pituitary gland or hypothalamus) or long-term treatment with corticosteroids.

Symptoms of adrenal cortex insufficiency

**Note:** Weakness, pigmentation, weight loss, dehydration, and hypotonia are leading symptoms of adrenal cortex insufficiency.

The range of symptoms is diversified and depends on the level of destruction in the adrenal cortex. Every stage from latent adrenal cortex insufficiency and a lack of symptoms up to endocrine coma are possible. People with latent (and unknown) adrenal cortex insufficiency are the most vulnerable.

Specific strain factors may lead to acute **decompensation of the hormonal situation called the Addisonian crisis.** Along with the aforementioned symptoms, other symptoms such as exsiccosis, hypotonic shock, pseudo-peritonitis, diarrhea, and vomiting, hypoglycemia with metabolic acidosis, delirium or even endocrine coma may occur.

The compensatory increase of melanocyte-stimulating hormone (MSH) levels can also result in darker skin pigmentation in individuals with primary adrenal cortex insufficiency.

**Diagnosing adrenal cortex insufficiency**

First, it is necessary to **determine the ACTH level in the plasma.** This increase is typical of Addison’s disease due to the compensatory efforts of the regulatory circuits. By
definition, secondary adrenal cortex insufficiency entails lower ACTH-plasma levels. Also, no increase in the ACTH level is possible with the corticotropin-releasing hormone (CRH) test.

The ACTH test is also used for diagnosis. In this test, the course of the serum cortisol level is observed before and after the administration of ACTH. Based on the pathophysiological considerations, an increase in cortisol after stimulation by ACTH with a primary adrenal cortex insufficiency is not possible. If secondary adrenal cortex insufficiency is present, stimulation with ACTH is still possible and increased cortisol levels can be observed.

**Note:** When secondary adrenal cortex insufficiency has been present for a long time, organ atrophy may eliminate simulatability.

Imaging procedures may be used to depict potential structural damage to the adrenal cortices as well as the search for autoantibodies in the case of Addison’s disease, for purposes of further aetiological clarification. It is also wise to monitor electrolyte levels.

**Note:** When assessing the laboratory parameters, one should note that in the case of primary adrenal cortex damage, all hormone sequences fail, whereas, with an ACTH deficiency, the function of the adrenal cortex can still be preserved. Aldosterone is further regulated in this case, and electrolyte disorders are relatively rare. Due to pituitary or hypothalamic defects, ACTH deficiency is also accompanied by other symptoms that affect other endocrinological systems such as the thyroid glands, ovaries, and testes.

**Differential diagnosis**

Admittedly, the symptoms of adrenal cortex insufficiency may be largely non-specific. One must consider other reasons for weight loss or weakness. Abdominal illnesses associated with diarrhea, vomiting or peritonitis must be taken into consideration. The potential side effects of medication are especially possible with electrolyte disorders. If an Addisonian crisis develops, all of the differential diagnoses for shock or acute abdomen are helpful and must be conducted systematically.

**Treating adrenal cortex insufficiency**

The hormone deficiency must be compensated. The hormonal circuits are highly complex. The physiological hormone states must frequently adjust to various situations, and they vary greatly. Infections, operations, and other bodily strains especially entail increased cortisol levels. Extensive training is an absolutely necessary part of the treatment concept for the patients to receive adequate hormone substitution.

**The following substitutions are useful:**

Glucocorticoids should be administered throughout the day according to the physiological secretion, whereby the highest daily dosage is taken in the early morning. The daily dosage amounts to about 15-25 mg hydrocortisone, can be selected individually and should be evaluated on a regular basis.

9a-fludrocortisone has proven to be useful against mineralocorticoid deficiency. The patient’s daily requirements also vary according to the age of the patient, and the medication is spread over 2-3 daily doses. The proper dosage can be determined by lab chemical electrolyte monitoring and normalized blood pressure (also under orthostatic conditions).

Every stress situation requires immediate adjustment of the dosage of hydrocortisone,
i.e., the **daily dosage must be increased 3-5 times**. An effective glucocorticoid must be administered parenterally to counteract complications (e.g., vomiting).

If women experience a loss of libido, the administration of dehydroepiandrosterone can be attempted.

The **Addisonian crisis is a medical emergency and requires urgent treatment**. Relevant blood samples must be taken quickly to determine the current health status. This is immediately followed by the calculated administration of sodium chloride (NaCl), glucose, and hydrocortisone. Continuous monitoring of the patient is also recommended.

NaCl and glucose amend corresponding deficiencies and simultaneously counteract hypovolemia. Amending the sodium deficiency must take place slowly to keep the risk of central pontine myelinolysis minimal.

**Note:** Infusion solutions containing potassium must not be administered!

Hydrocortisone is administered 1st as a bolus (100 mg intravenous (IV) and then as a prolonged infusion (200 mg/day).

In order to be able to immediately react to an Addisonian crisis, the patients must always have emergency medication available at hand. This includes, for instance, prednisolone suppositories. It is also sensible to provide them with an emergency ID.

**Phaeochromocytoma**

Phaeochromocytoma is a disease of the adrenal medulla. The adrenal medulla is a sympathetic ganglion made from catecholamine-producing cells. A tumor-like restructuring of these cells results in the excess production of adrenaline and noradrenaline. The patients are usually middle-aged when this disease sets in.

**Etiology of pheochromocytoma**

Pheochromocytomas are usually benign (approx. 85% of cases) and unilateral (approx. 90% of cases) tumors of the adrenal glands. More uncommon are the extra-adrenal forms, which are more often (up to 30%) malignant. Hereditary causes can usually be determined. This is how pheochromocytomas form during multiple endocrine neoplasias (MEN syndrome type 2), Von Hippel-Lindau syndrome or neurofibromatosis type 1.

**Symptoms of pheochromocytoma**

Pheochromocytomas are the cause of secondary hypertension affecting about 0.2% of all patients with hypertension. There are paroxysmal forms of hypertension due to acute hormone releases or persistent hypertonic circuit states from continuous hormone secretions.

The remaining symptoms are induced by the physiological effects of adrenaline and noradrenaline: vasoconstrictions result in pale skin, the stress reaction leads to glucose preparation in the blood, and an overall catabolic metabolic state causes weight loss. Leukocytosis is typically found in chemical laboratory tests.
Diagnosing pheochromocytoma

Pheochromocytoma must be considered for indications of secondary hypertension where patients do not have a normal nocturnal drop in their blood pressure, for treatment-resistant hypertension, and for sudden onset episodes of sweating, palpitations, and hypertensive urgency/emergency.

The diagnosis is made upon verification of catecholamine production. Influential medications for catecholamine (e.g., sympathomimetics of asthma treatment or sympatholytics e.g., alpha-blockers of benign prostate obstruction) should be dismissed in advance. Catecholamine levels can be analyzed by using various methods.

Increased metabolite measurements (metanephrine and normetanephrine) in the plasma (or 24 hours of collected urine) indicate pheochromocytoma.

The diagnosis is confirmed by the clonidine test. Physiologically clonidine inhibits the synthesis of adrenaline and noradrenaline. Autonomous overproduction eludes this inhibition.

The tumors can be located via endosonographic procedures or CT/MRT imaging. The scintigraphy or single-photon emission CT (SPECT) is often used to eliminate extra-adrenal tumors.

Additional clinical or genetic testing of the aforementioned syndromes for a possible hereditary cause may be sensible with verified pheochromocytoma.

Differential diagnosis

Pheochromocytoma falls into the sphere of differential diagnostic considerations of secondary hypertension. Along with many other considerations, hyperthyroidism must be particularly considered. In the event of a hyperglycemic metabolic state, diabetes mellitus and hypercortisolism must be ruled out. The ingestion of various drugs may also result in similar symptoms, and amphetamine or cocaine abuse must especially be investigated.

Treating pheochromocytoma

Removal of the tumorous structures is the treatment of choice. A minimally invasive laparoscopic adrenalectomy is often feasible. This requires a particularly cautious approach by the surgical team, as manipulations of the adrenal gland may lead to paroxysmal adrenaline release. This risk may be counteracted with a pharmacological sympathetic nervous system (SNS) blockage before the operation. The circulatory situation and blood sugar level must be continuously monitored during and after the operation.

If operative sanitation is not possible, normalization of the catecholamine level can be attempted via pharmacological measures. Phenoxybenzamine, prazosin or alpha-methyl-p-tyrosine are helpful.

Note: Sympatholytic monotherapy with beta-blockers is not suitable, as this negates the vasodilatory effect of the beta-receptors and may induce hypertensive crises!

The operative results are good. However, many patients tend to relapse. Thus, regular check-up examinations are necessary.