Essay title: Addison's disease presents with typical symptoms.
Describe the presenting features of this disease, and how they are explained by the underlying hormone deficiencies.

Abstract

Adrenal glands are small glands found on top of the kidneys. They produce specific hormones based on which layer they are made in the kidneys. These hormones work to increase blood volume, blood pressure and response to stress. Damage to the adrenal glands can cause hormonal deficiencies and this depends on the location of damage. Direct damage to the adrenals caused by our body's immune system is known as Addison's disease. It is a rare disease that can show signs of low blood pressure, vomiting, increased pigmentation and weight loss. Addison's disease has unclear features early on making diagnosis difficult. This leads to a later diagnosis and a more developed disease. Looking at the signs and linking them with the hormonal deficiencies helps explain their emergence. Blood tests provide vital information that can help reach the correct diagnosis of Addison's disease

Adrenal glands are small triangular shaped glands situated superiorly to the kidneys [1]. They act to produce hormones that aid in regulating crucial systems throughout the body such as metabolism, blood pressure and the immune system [1]. Hormones made by the adrenals are specific and are produced in different layers of the adrenals [1]. As mentioned, the adrenals serve an important role in maintaining normal bodily functions thus pathologic damage to the adrenals can result in a decreased production of these hormones resulting in a disruption to the balance created by the body's systems working synchronously. The specific hormonal deficiencies are dependent on the location of damage causing primary, secondary, or tertiary adrenal insufficiency [2]. Addison's disease (AD) is termed as an acquired primary adrenal insufficiency and is named this way due to an autoimmune process causing it [3]. The rarity of the disease coupled with its common symptoms give rise to a difficult diagnosis to reach which sprouts the need for a high clinical suspicion during a patient history to avoid a misdiagnosis or a later one [3]. In light of this, this essay will give an outline on the adrenal glands and the hormones they produce before focusing more on AD by providing an insight into the pathophysiology and aetiology of the disease. The diagnosis of AD will be expanded upon as well as the clinical presentations of the disease. Moreover, the essay will address the link between the hormonal deficiencies and their clinical appearance.

The adrenal glands are composed of different layers that act to produce specific hormones that regulate numerous bodily functions. The triangular shaped gland as well as its position on the kidneys can be seen in fig 1. Furthermore fig 1. portrays the 3 distinct layers in question within the cortex. It is important to note that each layer uses cholesterol as a precursor to produce their respective hormones [5]. Starting with the

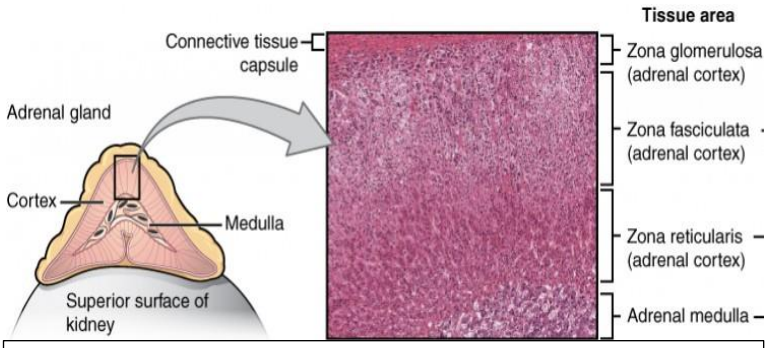

Figure 1 (fig 1): Adrenal glands coupled with its histology, portraying the different layers [4]

outermost layer, the zona glomerulosa produces mineralocorticoids such as aldosterone which acts on the kidneys to increase circulating volume and blood pressure [5]. This is

achieved through increased synthesis of epithelial sodium channels (ENaC) and sodium-potassium ATPases on nephrons [5]. This process results in increased sodium reabsorption and potassium excretion leading to increased water reabsorption as a result. The middle layer, known as the zona fasciculata produces glucocorticoids such as cortisol [5]. Glucocorticoids have numerous functions and play a vital role in increasing the body's ability to respond to stress [5]. Glucocorticoids like cortisol act to upregulate genes that stimulate numerous systems such as metabolism, the immune system, and the cardiovascular system [5]. The secretion of cortisol opposes the effects of insulin leading to increased gluconeogenesis and decreased glucose uptake thereby increasing serum glucose for use during stress responses [5]. Zona reticularis is the innermost layer and produces androgen precursors like dehydroepiandrosterone (DHEA) [5]. These precursors need to be converted into their active form in peripheral tissues and they play a major role during puberty [5]. The adrenal medulla is involved in the synthesis of catecholamines, adrenaline and noradrenaline [5]. These hormones act on the sympathetic nervous system to assist in executing the fight-or-flight response which is achieved through the increase of blood pressure in vascular smooth muscle through alpha-1 receptors [5]. Glucagon secretion is stimulated via beta-2 receptors and insulin is reduced via alpha-2 receptors [5]. This brings about the activation of glycogenolysis resulting in an increase in serum glucose which can be utilised during a sympathetic response [5]. The importance of healthy adrenal glands becomes noticeable when taking what was mentioned into consideration and damage to its structure and integrity can lead to deleterious effects consequently.

Damage to the adrenal glands can have a negative impact to its ability to secrete enough hormones as required. When this occurs, it is known as adrenal insufficiency [2]. Fig 2. gives an outline on the hypothalamic-pituitary-adrenal axis (HPA) which depicts the order of hormonal activation as well as what is affected based on the type of adrenal insufficiency. Primary adrenal insufficiency is portrayed as direct damage to the adrenal cortex resulting in a decrease in mineralocorticoids and glucocorticoids [2]. Secondary adrenal insufficiency is shown as damage to the pituitary gland causing decreased adrenocorticotropic hormone (ACTH) [2]. This results in a decrease in glucocorticoids but not mineralocorticoids since hormones such as aldosterone are primarily regulated by the renin-angiotensin system [2]. Tertiary adrenal insufficiency is caused by damage to the hypothalamus resulting in decreased pituitary stimulation from corticotropin releasing hormone (CRH) to release ACTH [2]. Glucocorticoids are reduced but aldosterone is also preserved here due to the damage not affecting the renin-angiotensin system [2]. AD is an acquired primary adrenal insufficiency resulting in a decrease in cortisol, aldosterone, and androgens [3]. AD is rare which is evident from its incidence of 0.6 per 100,000 per annum [3]. Numerous causes can be attributed to this disease such as sepsis, tuberculosis, and other autoimmune conditions [3]. Autoimmune conditions such as type 1 diabetes and vitiligo increase the risk of AD developing [3]. In AD the immune system attacks the adrenal cortex through the production of autoantibodies against 21-hydroxylase enzyme and this process can be seen in 90% of cases [3]. This enzyme is crucial during the conversion of mineralocorticoid and glucocorticoid hormones into their active forms therefore the inclusion of autoantibodies will result in decreased aldosterone and cortisol [3]. By gaining a better understanding of the physiology behind AD, medical professionals can justify the presentations and

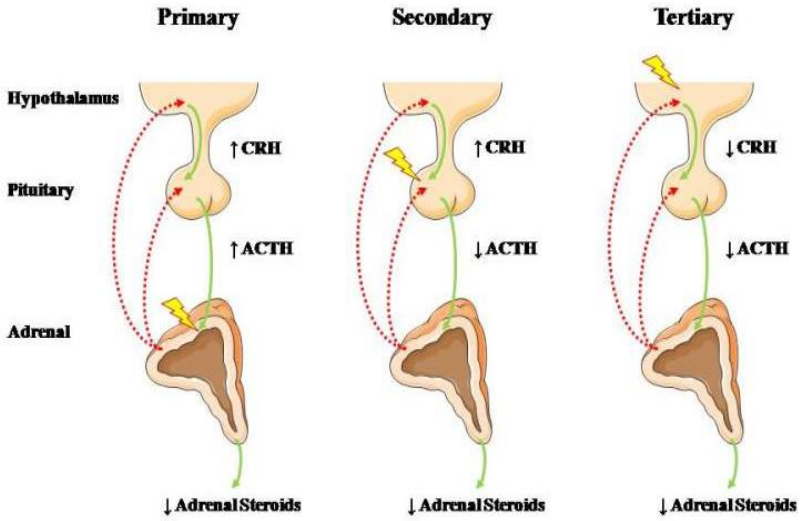

Figure 2 (fig 2): Hypothalamic-pituitary-adrenal axis and site of injury for the type of adrenal insufficiency [2]

appearance of the disease. This is vital in drawing a sensible conclusion and bringing out a reasonable diagnosis especially with the insidious nature of the disease.

The consequences that follow adrenal insufficiency becomes evident with the information provided which helps draw a link between the presentation of the disease and the underlying physiological changes. Patients with AD often present with weakness and hypotension in the early stages [6]. The nonspecific nature of these symptoms are often why patients with AD receive a later diagnosis than anticipated, allowing the damage to progress further, resulting in worsened signs and symptoms [6]. As the disease progresses other symptoms can include nausea, vomiting and diarrhoea [6]. Hyperpigmentation, shown in fig 3. Is one of the signs visible in patients with AD [6]. Increased pigmentation can be seen around the 4 images with an addition of vitiligo being noted in the bottom right image. Other signs can include weight loss and anaemia [6]. With AD's subtle nature and its nonspecific symptoms, the difficulty of its diagnosis becomes apparent especially when factoring in that a study investigating patients with AD found that 40% received their diagnosis more than 6 months after symptoms emerged [7]. Even though the sample size of 426 patients is not large enough to draw a conclusive argument, it does set the importance for a cautious mindset when taking a patient's history [7]. This disparity is further reinforced in another study that found 60% of patients that had AD received their confirmed diagnosis only after repeated visits to numerous clinicians [8]. The impression is given that many cases are recognised once an acute adrenal crisis occurs in these patients, which is classified as signs of hypotension, hyponatraemia, hyperkalaemia, and hypoglycaemia [8]. This is problematic as an adrenal crisis can be fatal if not recognised and treated, as it can depict the first presentation of AD [8]. Whilst undertaking the patient history, the medical professional must uphold their observational skills when looking at the patients' general demeanour. Signs of discomfort, pain and generalised weakness can indicate the need for further investigation [3]. Inspection of the skin should be commenced

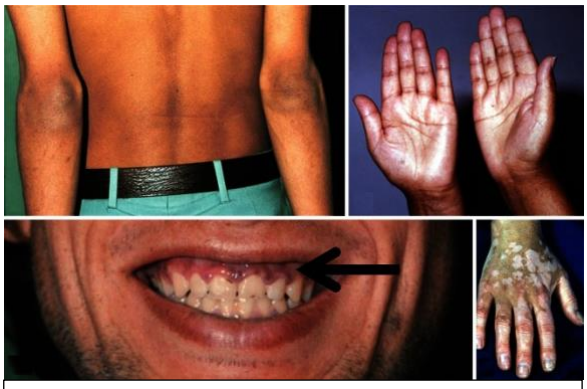

Figure 3 (fig 3): Clinical presentation of patients with Addison's disease [6]

with a closer look into sun-exposed areas such as the palmar and dorsal surface of the hand for hyperpigmentation or vitiligo, as shown in fig 3 [3]. Taking this into account among other unexplained symptoms such as poor appetite and fatigue, medical professionals can use this information to emphasise the link between these presentations and the underlying physiological changes [3]. This would prove useful in furthering our understanding of why these hormonal changes are causing the emergence of these signs and symptoms.

By factoring in the clinical presentation with the hormonal deficiencies we can draw links that further our understanding of AD to help us confirm or deny any suspicions about what disease it could be. In AD, excess ACTH from the anterior pituitary gland is secreted to stimulate the damaged adrenal cortex [7]. It is important to note that ACTH is derived from the proopiomelanocortin (POMC) which also produces melanocyte stimulating hormone (MSH) [7]. Based on this, the appearance of hyperpigmentation can be attributed to the increased stimulation of skin melanocytes by ACTH and MSH [7]. This is not the case in secondary adrenal insufficiency due to the decreased levels of ACTH [7]. Blood pressure can be measured and in the case of patients with AD, hypotension is usually what is shown [7]. This in addition with salt cravings are common characteristics of AD and are explained by the decreased levels of aldosterone in these patients [7]. We can expect this decrease due to the mineralocorticoid deficiency that is evident in AD. Furthermore, the 4 signs designated to an adrenal crisis can also be attributed to the decreased levels of mineralocorticoids [7]. When regarding other symptoms previously mentioned such as weight loss and vomiting, the notion was made that the decreased production of glucocorticoids was linked with the appearance of these symptoms [7]. By compiling these explanations, we can construct these links and justify the underlying cause of these presentations. A more detailed approach, however, is necessary when delving deeper into these investigations which reinforces the need to commence further tests during our diagnosis of AD.

When considering which tests to conduct for any given disease, a blood test is usually a common option to go for when considering the accessibility and the type of information

shown in them. For patients with AD, we can expect a blood test to show high levels of renin to compensate for the decreased aldosterone levels [9]. Electrolytes such as sodium and potassium are measured, and we can expect a decreased and increased concentration respectively [9]. This is due to the lowered aldosterone levels which causes decreased sodium reabsorption, increased potassium, and water excretion. This would result in hypovolaemia, which would help explain the hypotension and would further suggest adrenal insufficiency [9]. A cortisol test may be requested upon suspected AD [9]. Due to the diurnal pattern that cortisol follows, an early morning level is obtained preferably, however, this is not always the case especially in an emergency [9]. This sets up the importance to remain vigilant of this fluctuation in cortisol levels depending on when it was taken. A decreased cortisol level would be shown in AD due to the glucocorticoid deficiency resulting in decreased cortisol production [9]. To evaluate adrenal insufficiency further and provide a distinction between the different types, an ACTH stimulation test can be given. Plasma cortisol levels are measured directly after ACTH administration and 30 to 60 minutes into the test [9]. In AD, ACTH is already markedly elevated, and this is further emphasised with high CRH stimulation [9]. This will still not be able to stimulate cortisol secretion which would help confirm primal adrenal insufficiency, as opposed to secondary adrenal insufficiency where ACTH will remain low [2]. It is important to note that the negative feedback loop between glucocorticoids, CRH and ACTH is weakened due to the insufficient production of glucocorticoids in AD [2]. Adrenal antibodies such as 21-hydroxylase antibodies can be tested, and a positive result can help diagnose AD [9]. A diagnosis of AD is set when the results portray low levels of cortisol and aldosterone, high levels of renin and a blunt cortisol response with ACTH stimulation [3]. More tests can include imaging such as a magnetic resonance imaging to assess the size and shape of the adrenal glands, and for AD we can expect a normal or decreased size [9].

With all that has been mentioned, medical professionals are able to connect the underlying hormone deficiencies with the presenting symptoms of AD and can justify this link extensively based on the hormone's intended function. The outline of the adrenal glands provided a foundation to the normal physiology of the glands and helped portray the

consequences that followed the site of injury. An overview around the types of adrenal insufficiency have been addressed to provide certain distinctions between them. Whilst a clear link between the presentation of AD and its hormonal deficiencies has been addressed, the need for improving diagnostic accuracies becomes apparent when taking delayed and incorrect diagnoses into account. Moving forward medical professionals must take a more cautious approach when trying to diagnose AD. By exposing themselves to more cases involving AD, medical professionals can detect subtle signs shown during a patient history which can be invaluable in reaching the correct diagnosis.

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