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An Update on Addison's Disease

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ABSTRACT

Addison's disease – the traditional term for primary adrenal insufficiency (PAI) – is defined as the clinical manifestation of chronic glucocorticoid- and/or mineralocorticoid deficiency due to failure of the adrenal cortex which may result in an adrenal crisis with potentially life-threatening consequences. Even though efficient and safe pharmaceutical preparations for the substitution of endogenous gluco- and mineralocorticoids are established in therapy, the mortality in patients with PAI is still increased and the health-related quality of life (HRQoL) is often reduced.

PAI is a rare disease but recent data report an increasing prevalence. In addition to the common "classical" causes of PAI like autoimmune, infectious, neoplastic and genetic disorders, other iatrogenic conditions – mostly pharmacological side effects (e. g., adrenal haemorrhage associated with anticoagulants, drugs affecting glucocorticoid synthesis, action or metabolism and some of the novel anti-cancer checkpoint inhibitors) are contributing factors to this phenomenon.

Due to the rarity of the disease and often non-specific symptoms at least in the early stages, PAI is frequently not considered resulting in a delayed diagnosis. Successful therapy is mainly based on adequate patient education as a cornerstone in the prevention and management of adrenal crisis. A focus of current research is in the development of pharmacokinetically optimized glucocorticoid preparations as well as regenerative therapies.

Introduction

The clinical picture of primary adrenal insufficiency (PAI) is based on the chronic deficiency of glucocorticoids and/or mineralocorticoids due to failure of the adrenal cortex to produce these hormones in sufficient amounts. Since they are essential regulators of water- and electrolyte homeostasis as well as energy balance, PAI is a very severe disease and may result in acute and potentially life-threatening adrenal crisis [1]. The dramatic consequences of adrenal failure with weakness, weight loss, anorexia, orthostatic hypotension due to dehydration, salt craving, hyperpigmentation, mus-

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culoskeletal and abdominal pain, nausea, vomiting, and ultimately the lethal outcome have first been recognized by Thomas Addison, a british surgeon – therefore, PAI is also commonly named as "Addison's disease" [2].

The prognosis of the disease dramatically improved with the availability of steroid hormones for treatment and the development of feasible diagnostic tests. After successful isolation and characterization of cortisol and cortisone [3–6] and the establishment of techniques to synthetize glucocorticoid hormones [7], the treatment of adrenal insufficiency as well as the diagnosis of the disease was substantially promoted mainly by the clinical work of Wilder in the 1930's and then Thorn and Forsham in the 1940s and 1950s [8–10].

Here, we will provide an overview on current aspects in the diagnosis and treatment of Addison's disease. Subsequently, as a synonym of Addison's disease, we will exclusively use the term PAI for reasons of stringency and convenience.

Epidemiology and Etiology of Primary Adrenal Insufficiency

PAI is a rare disease with a current prevalence in our Western societies of about 100–140 cases per million [11]. However, the reported number has substantially increased over time from 40–70 cases per million in europe in the 1960s [12]. Interestingly, recent data suggest a continuation of this trend with a further increasing prevalence of PAI particularly in women [13]. In addition to a real increase of the prevalence the possibility should be considered that this phenomenon may be related to a general underestimation of the prevalence of PAI in the past and improvements of diagnostic and health care conditions over time [14]. It is also possible that etiologic changes may contribute to this observed effect. As described by Addison, based on 11 patients, the etiology of adrenal destruction in PAI was originally more than 50 % tuberculosis, 30 % neoplastic/metastatic and about 10 % haemorrhagic at that time [2]. Today, in western societies, 80 % of PAI is caused by autoimmune adrenalitis followed by tuberculosis or other infectious diseases (e. g. HIV/AIDS, CMV, candidiasis, histoplasmosis, syphilis and others) and malignant diseases (e. g. lung, breast, colon cancer and others) in about 10 % of cases. The remaining causes include (bilateral) adrenalectomy (e. g. for Cushing's syndrome or adrenal tumours), genetic diseases (e. g. congenital adrenal hyperplasia (CAH), adrenal hypoplasia congenita, Adrenoleukodystrophy in males) and adrenal haemorrhage (e. g. Waterhouse-Friderichsen-Syndrome in sepsis) [15–17].

PAI due to autoimmune adrenalitis may exist in isolation, but more than 50 % of autoimmune adrenalitis occurs in combination with other autoimmune disorders as part of autoimmune polyglandular syndromes (APS). These syndromes sometimes have a known specific genetic background (e. g. AIRE gene mutations in APS type 1) but all forms of autoimmune adrenalitis show some association with specific gene variants of the major histocompatibility complex (e. g. HLA-DR3) or genes encoding for proteins involved in mechanisms of immunological regulation (e. g. CTLA-4). This emphasizes the central role of T-cell and cellular immunity in the pathophysiology of Addison's disease [18–21].

Due to the increasing age in our population with chronic illness often requiring complex medical treatment and polypharmacy, pharmacological adverse effects (e. g., adrenal haemorrhage associated with anticoagulants, drugs affecting glucocorticoid synthesis, action or metabolism like specific antimycotics and other compounds) are becoming more and more relevant as potential predisposing factors contributing to the manifestation of PAI [16]. This is distinct from the even more common scenario of secondary adrenal insufficiency (i. e., hypothalamic-pituitary suppression) of chronic glucocorticoid use for inflammatory conditions. Further, it is of increasing importance that novel drugs and therapeutic regimens may induce the manifestation of immune-mediated endocrine disorders including PAI. For example, recent pharmacovigilance data indicate an association of PAI with the use of different immune checkpoint inhibitors (ICIs), a novel class of drugs applied for the treatment of a variety of malignant tumours [22, 23]. Interestingly, it has been reported that PAI may develop as a late adverse event even more than a year after discontinuing treatment with pembrolizumab, a prototypic ICI [24]. Therefore, it is essential to carefully monitor patients being treated with drugs associated with an increased risk for the development of PAI and other immune-mediated endocrinopathies.

Unfortunately, symptoms and signs of PAI are non-specific in the early stages, therefore making the clinical diagnosis of PAI very difficult. Further, due to the fact that PAI is a rare disease with a reported incidence of 4–6 cases per million per year, the diagnosis is frequently not considered and therefore delayed [25, 26]. As a consequence, the first presentation of many patients with PAI is an acute and potentially life-threatening adrenal crisis in the emergency department.

Diagnosis of Primary Adrenal Insufficiency

PAI should be suspected in all acutely or chronically ill patients with general fatigue or severe weakness and unexplained dehydration, hypotension, weight loss, fever, abdominal pain and hyperpigmentation. Hyponatraemia, hyperkalaemia and - especially in children - hypoglycaemia are key lab characteristics of the disease reflecting the deficiency of gluco- and mineralocorticoids [27]. The diagnostic threshold should be even lower when patients have features of other autoimmune diseases like vitiligo, type-1-diabetes or autoimmune gastritis/Vitamin B12-deficiency. Additionally, in acutely ill patients with chronic infectious diseases – in particular HIV, CMV or tuberculosis – or in patients receiving drugs interfering with cortisol synthesis, action or metabolism - in particular anticonvulsants (carbamazepine, phenytoin), anti-fungals (ketoconazole), anti-cancer drugs (abiraterone, mitotane, ICIs) or specific over-the-counter medicines (e. g. St John's Wort) - the index of suspicion should be high [16, 27].

In patients with symptoms and signs indicative of PAI, further diagnostic testing is required. Initially, a random blood sample for the simultaneous determination of ACTH and cortisol before glucocorticoid treatment is essential for the detection of glucocorticoid deficiency which is usually the leading clinical characteristic. The typical constellation in PAI is a low cortisol serum concentration in combination with an elevated ACTH. As a generally accepted clinical rule, PAI is regarded as very likely if cortisol is < 5 µg/dl (138 nmol/L) with a concomitant ACTH increased more than 2-fold over the upper limit of the normal range [27, 28]. Mineralocorticoid deficiency is typically reflected by decreased sodium and ele-

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vated potassium serum concentrations. To verify mineralocorticoid deficiency, determination of plasma renin and aldosterone may be useful if there is no hyperkalemia present. The combination of an elevated plasma renin together with a normal or low serum aldosterone concentration is suggestive of mineralocorticoid deficiency [27, 29, 30].

Dynamic testing of the adrenocortical function with the corticotropin stimulation test – also termed as cosyntropin test, ACTH test or Synacthen test - is currently the best established and validated method for the diagnosis or exclusion of PAI [31]. If the diagnosis is not already obvious, this test may be performed as a confirmatory test if available and the patient is stable enough [27]. In this test, adults usually receive an injection of 250 µg intravenous (or alternatively intramuscular; in children < 2 years 125 µg) of tetracosactide, a peptide representing the sequence of the first 24 (out of a total of 39) amino acids of ACTH and cortisol is determined immediately before and then 30 and 60 min after injection. As a common cut-off for the diagnosis of (primary) adrenal insufficiency, a peak cortisol concentration of less than 500 nmol/l (18 µg/dl) after stimulation is historically widely accepted [27]. However, cut-off levels for cortisol and other adrenal steroids after stimulation with cosyntropin may differ significantly based on the method used for detection (Liquid chromatography tandem mass spectrometry (LC-MS/MS) vs. immunoassay) [32]. Clinicians are strongly urged to consult with the local clinical chemist to verify the assay-specific definitions of normal cortisol responses to stimulation.

In contrast to the "high-dose" (250 µg) corticotropin test, the so-called "low-dose" corticotropin stimulation test utilizes 1 µg tetracosactide as a variation [33, 34]. The advantages and disadvantages of both tests in the diagnosis of adrenal insufficiency have been extensively discussed [35, 36]. Since both tests give comparable results for the serum cortisol concentration at least 30 min after stimulation and based on the fact that the "high-dose" (250 µg) corticotropin test is more comprehensively validated compared to the "low-dose" (1 µg) corticotropin test, it is suggested to perform the "low-dose" (1 µg) corticotropin test in the diagnosis of PAI only when the substance is in short supply [27, 34, 35, 37, 38].

Although a clear cut-off (500 nmol(l (18 µg/dl), as determined with common immunoassays) for the stimulated serum cortisol concentration has been defined to diagnose or exclude (primary) adrenal insufficiency, interpretation of the cosyntropin-test may be complicated by several factors. For example, the level of the binding globulin for cortisol, CBG, is increased by estrogens (e. g. in pregnancy or in oral contraceptives) – thereby resulting in increased measured cortisol levels, while patients with several disorders (e. g. liver disease or nephrotic syndrome) may have lower levels of measured cortisol due to decreased levels of CBG [39–41]. Concomitant or surreptitious use of synthetic glucocorticoids (administered orally or topically or inhaled) may also confound the results depending on the specificity of the cortisol assay in use. Therefore, especially in medically complex patients and pregnant women, diagnosis and interpretation of test results requires extensive experience in clinical endocrinology.

Once PAI has been confirmed at the biochemical level, further diagnostic testing (e. g. 21-OH antibody, 17-OH-progesterone, CT adrenals, very long chain fatty acids (VLCFA) in preadolescent boys) to determine the etiology of the disease (autoimmuneadrenalitis, CAH, infections, infiltrative disease, adrenoleukodystrophy…) is suggested, since this may have prognostic and therapeutic implications [27].

Treatment and Prevention of Primary Adrenal Insufficiency

Hydrocortisone is the drug of choice for the replacement of glucocorticoids. In adults, the usual dose is 15–25 mg/d given orally in 2 or 3 doses with the highest dose in the morning to mimic circadian rhythm [27]. The first dose should be taken with awakening early in the morning whereas the last dose should be taken at the latest 4–6 h before sleep to avoid insomnia and nocturnal insulin resistance with potential adverse metabolic consequences [42]. As an alternative to hydrocortisone, 3–5 mg/d prednisolone as a single dose or in 2 divided oral doses is suggested. This may be favourable in patients requiring a simplified therapeutic regimen due to specific individual circumstances – e. g. to improve comfort and compliance [43]. Dexamethasone should not be used due to its non-physiological pharmacokinetic properties (long half-life) and the resulting risks for adverse metabolic effects such as dyslipidaemia, hyperglycaemia and diabetes [44, 45]. In children, only hydrocortisone should be used for replacement therapy because its short half-life allows for best control; a typical starting dose is about 8 mg/m^2 divided in 3 doses. Also, in pregnancy, hydrocortisone is the preferred drug for glucocorticoid replacement. In the last trimester of pregnancy, cortisol levels and free cortisol rise significantly, therefore it is suggested to increase the hydrocortisone dose by about 30 % in the last trimester in pregnant patients with PAI [27, 46, 47]. Further, since high levels of progesterone counteract mineralocorticoid action, an increase of the fludrocortisone dose based on blood pressure and electrolyte status is frequently required especially in the third trimester.

Monitoring and management of glucocorticoid replacement therapy is primarily based on clinical parameters such as body weight, oedema, blood pressure, cushingoid changes as well as mental and physical performance. It is of prime importance to prevent and detect inadequate dosing and metabolic complications of long-term glucocorticoid treatment [48, 49]. In children, this includes monitoring of general development and growth velocity every 3–4 months. Laboratory measures of plasma ACTH and random serum cortisol are of little value. For example, patients with adequate hydrocortisone replacement frequently show increased ACTH levels because the short half life of orally administered hydrocortisone rarely fully mimics physiologic secretion to the point of normalization of all ACTH measures. In addition, the glucocorticoid dose needs to be adjusted dynamically according to specific stressful circumstances. For example, in acute febrile illness with temperatures exceeding 38 °C the oral hydrocortisone dose should be increased 2–3 fold. For major surgery or in adrenal crisis, hydrocortisone should be given intravenously at an initial dose of 100 mg in adults (50 mg/m^2 in children) followed by a continuous infusion of 200 mg hydrocortisone (50–100 mg/m^2 in children) over 24 h together with intravenous fluid replacement to counteract dehydration [27, 50]. Due to volume depletion (salt wasting), hypotension and circulatory failure, acute adrenal crisis is a life-threatening condition. If adrenal crisis is suspected, a random cortisol and ACTH

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may be measured but therapy should then be instituted without the delay of awaiting results.

In mineralocorticoid deficiency, fludrocortisone is the drug of choice to stabilize water- and electrolyte balance. A common starting dose is 50–100 µg/d in children and adults with PAI, typically given orally once in the morning. Patients should be encouraged to include salt in their diet. Monitoring and management of mineralocorticoid replacement therapy is mainly based on clinical parameters like salt craving, oedema, blood pressure in combination with lab parameters like normal sodium and potassium concentrations in the serum; a plasma renin in the upper reference range is regarded as a helpful indicator for fine-tuning [29, 51–53] but should not supersede clinical assessment. Stress adjustment of mineralocorticoid replacement is not required.

In addition to the replacement with gluco- and mineralocorticoids which are vital, androgen substitution with dehydroepiandrosterone (DHEA) is frequently discussed in women with PAI. Based on current data, DHEA replacement may be considered in women receiving optimal gluco- and mineralocorticoid therapy that are still suffering from symptoms like low libido and depressive symptoms [27, 54, 55], particularly if post-menopausal or having concomitant primary ovarian insufficiency with loss of ovarian androgens.

Important and frequently discussed questions concern health related quality of life (HRQoL), co-morbidities and prognostic factors in patients with PAI. In this group of patients, self-reported quality of life has been documented to be lower as compared to the general population [56]. In addition, patients with PAI reportedly have a higher incidence of affective disorders such as depression and anxiety as well as a higher odds ratio for metabolic disorders like diabetes mellitus as compared to controls. This is reflected by more frequent hospital stays and substantially higher health care expenditures in these patients [49, 57–59]. Further, increased mortality has been reported in patients with PAI; in particular acute infections carry a risk of fatal adrenal crisis [11, 56, 60, 61]. However, other factors such as the impact of potentially adverse cardiovascular risk profiles related to excessive glucocorticoid replacement regimes have been discussed in this context [45, 59].

In patients with known PAI, preventing adrenal crisis is of central importance. Currently, the reported incidence is about 6-8/100 patients per year with a mortality rate of 0.5/100 patient years [62, 63]. Therefore, patient education with regard to the management of specific situations requiring an increased glucocorticoid dose (e. g. flu-like febrile infections) including the use of techniques for parenteral administration of emergency glucocorticoids, as well as recognition of symptoms and signs signaling an emerging adrenal crisis is essential [27, 50]. Further, it is recommended that all patients with PAI should carry a medical alert notification or even better, a steroid emergency card to inform physicians and other medical personnel [27]. A standardised European emergency card for patients with PAI has been endorsed by the European Society of Endocrinology (ESE) and is sponsored by a variety of institutions [64].

Novel Aspects And Current Developments For the Treatment of Primary Adrenal Insufficiency

Steroid substitution in patients with PAI is effective but glucocorticoid replacement still has clear pharmacological limitations and normal physiology can not be completely mimicked by using oral hydrocortisone. In order to improve the pharmacokinetic properties and to better provide circadian cortisol concentrations with a morning peak, a dual-release preparation of hydrocortisone that needs to be given as a single oral dose in the morning has been developed [65]. Early clinical data are promising with regard to drug efficacy and safety [66]. In addition to more patient satisfaction due to the single-dose application, favourable effects with regard to body weight, blood pressure and glycaemic control have been described as compared to standard therapy [67, 68]. Other modified-release hydrocortisone formulations are currently in clinical development [69]. A challenging problem is glucocorticoid replacement in children; in order to help improve dosage and oral application, hydrocortisone capsules have been developed and successfully tested [70]. Restoration of normal circadian cortisol concentrations in patients with PAI compared to oral regimens may be accomplished by continuous subcutaneous cortisol infusion using insulin pumps. Although this approach is complex and therefore only applicable in selected individual patients, initial reports appear very promising [71–73].

Other experimental approaches in very early stages have been described including immunosuppression in patients with early forms of autoimmune adrenalitis, gene therapy for monogenic forms of PAI, transplantation and cell replacement as well as reprogramming techniques to induce a steroidogenic phenotype from cells of different origin [74–78].

In summary, PAI is a critically important and potentially life threatening disease but with modern therapy and education, affected patients can now return to a highly functional status. Further improvements are still needed to improve both quality of life and unravel potential disease mechanisms that may be exploited for possible prevention or cure of this serious disease.

Conflict of Interest

No conflict of interest has been declared by the authors.

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