PERSPECTIVE ARTICLE

Addison's disease with autoimmunity

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ABSTRACT

A uncommon condition known as Autoimmune Addison Disease (AAD) is brought on by an immune system attack on the adrenal cortex. Autoantibodies against 21-hydroxylase (21-OH), a steroid enzyme expressed in the adrenal cortex, are frequently seen in patients with AAD. Adrenal steroid hormone insufficiency results from the adrenal glands being destroyed by the autoimmune onslaught. AAD is fatal if left untreated, however modern hormone replacement medication makes it possible to live. Treatment options include the replacement of glucocorticoids and mineralocorticoids, while the value of androgen replacement is questionable. Since existing oral replacement regimens produce intervals of supraphysiological and infraphysiological cortisol levels, the ideal glucocorticoid replacement therapy would replicate the natural diurnal cortisol cycle. However, this is not practical to do. To more accurately mimic the diurnal cortisol profile, a modified-release hydrocortisone tablet with an immediate-release coating and an extended-release core was produced in recent years.

There is worry that patients frequently get excessive amounts of glucocorticoids, which can have detrimental effects on the heart and metabolism (such as reduced glucose tolerance and dyslipidemia). Aldosterone and 11-deoxycortison, the two natural mineralocorticoids, are not appropriate for replacement treatment; instead, the synthetic corticosteroid fludrocortisone is employed.

The increasing mortality and morbidity recorded for individuals with AAD may be attributed to today's replacement treatment, which is far from physiological. AAD frequently co-occurs with autoimmune polyendocrine syndrome and other Organ-specific Autoimmune Diseases (APS). Mutations in the Autoimmune Regulator (AIRE) gene lead to the extremely uncommon monogenic illness known as APS-1. Chronic mucocutaneous candidiasis, hypoparathyroidism, and AAD are the three symptoms that define APS-1. AAD, autoimmune hypo- or hyperthyroidism, and type 1 diabetes (T1DM) are only a few examples of the $2 concomitant autoimmune endocrinopathies that characterise the much more widespread and genetically complicated APS-2 entity. An essential technique in patient monitoring is autoantibody screening, which can reveal the existence of or anticipate the onset of other autoimmune illnesses. Autoantibodies directed against 21-OH are a good diagnostic marker of AAD. Due to AAD's rarity, most studies have been too small to accurately assess the disease's natural course and comorbidities. The Swedish Addison Registry (SAR), which now has 813 people, is the world's biggest collection of clinical data and blood samples from patients with AAD. 660 AAD patients who were enrolled in the registry from 2008 to 2014 and who made up around 50% of all AAD patients in Sweden were characterised clinically and immunologically using the SAR. Our goal was to learn more about cardiovascular risk factors, replacement treatment, immunological profile, and comorbidities associated with autoimmune diseases.

Key Words: *Pancreatectomy; Pneumoperitoneum; Pancreatic resections*

PRIMARY INSUFFICIENCY OF THE ADRENAL GLANDS

Primary adrenocortical insufficiency, also known as Addison's Disease (AD), is caused by the bilateral destruction or dysfunction dysfunction of the adrenal cortex. The biochemical pattern of this condition is a deficiency in the production of glucocorticoids, mineralocorticoids, and androgens, which is accompanied by high levels of both ACTH and plasma renin activity.

Number of AD cases

By the end of the 1990s, there were 93 cases to 144 cases of AD per million people in Europe, up from 40 cases to 70 cases per million people in the 1960s. 162 Betterle-Morlin cases have been reported during the last century and in more recent years, with an estimated frequency of 4 new cases per million people year. During the first part of the twentieth century, TB was the most prevalent cause of AD in Europe, but autoimmune AD has become the most common form of AD in recent years. The recent rise in AD cases, which has coincided with a drop in TB incidence, is an indication of the increased percentage of autoimmune AD patients. In our series of 615 AD patients gathered from 1969 to 2009, the autoimmune form was identified in 501 cases (81.5%), the tuberculosis-related form in 9%, and the remaining 8% of cases were attributed to other causes, such as infections, genetics, infiltrative diseases, primary and secondary cancers, drugs, or surgery-induced hypoadrenalism.

The prevalence of the hereditary forms of AD is more common in the paediatric population than it is in the adult population, which shows a significant difference in the frequency of the various disease manifestations. Congenital adrenal hyperplasia accounted for 71.8 % of the cases in a study of 103 cases of AD seen at the Pediatric Endocrinology Service in Quebec (Canada) over a 20 year period

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(1981–2001), while other genetic forms accounted for another 5.9%, the autoimmune forms for only 12.7%, and the remaining cases were of unknown cause.

Histopathology

The adrenal glands are tiny and weigh just 1 g to 2 g in patients with autoimmune AD, making it challenging to see them on imaging or detect them during an autopsy. The cortex is often atrophic and infiltrated with mononuclear cells that include lymphocytes, plasma cells, macrophages, and sometimes cells with germinal centres. The medulla's cells are normal and uninfiltrated, in contrast to the other adrenocortical cells, which are hyperplastic and encircled by lymphocytes. Fibrosis comes in different intensities. Only 5% of the invading cells are B cells, and the majority of them 95% are T cells with a CD4/CD8 ratio of 5-6/1. Nearly half of them have class II HLA positivity.

Cellular immunity

Patients with AD of recent start have been shown to have higher amounts of circulating Ia-positive T cells, and a proliferative T-cell response to an 18 kDa to 24 kDa molecular weight adrenal–specific protein fraction has been shown. Patients with autoimmune AD in the setting of an Autoimmune Polyglandular Syndrome (APS) type 2 have also been observed to have a deficient suppressor function of human CD4+/CD25+ regulatory T cells, but not in patients with autoimmune AD alone. Recent research has shown that individuals with autoimmune AD have circulating peripheral blood mononuclear cells that can be stimulated by the enzyme 21-OH and more specifically by the amino acids 342-361 of the enzymatic molecule, which may be a specific disease epitope represented by cells expressing the HLA-DRB1*0404 allele. IFN and IL-2 may be produced in vitro by these cells when they are stimulated by 21-OH peptides.

Animal models

By injecting adrenal extracts into rats, an experimental adrenalitis was induced that was characterised by a mononuclear cell infiltration, adrenal cortex insufficiency, and circulating antibodies against adrenal tissue. Passive transmission of this illness was also induced in these animals by lymphoid cells. However, the presence of adrenal Cortical Autoantibodies (ACA) was never mentioned in the reports of a spontaneous form of autoimmune AD in dogs and cats. In the absence of overt symptoms of hypoadrenalism, the adrenal cortex of NOD (Non Obese Diabetic) mice, which acquire type 1 diabetes mellitus on their own, may also have a mononuclear cell infiltration.

Humoral immunity

Autoantibodies to the Adrenal Cortex (ACA)

In 1957, autoantibodies to adrenal cortical extracts were found in 25% of 'idiopathic' AD patients. Following that, ACA were found in 51% of individuals with autoimmune AD using the traditional indirect immunofluorescence approach on thin slides of adrenal cortical tissue. These antibodies are directed against a microsomal autoantigen found in the cytoplasm of all 3 cell layers of the adrenal cortex and are organ but not species-specific. The immunofluorescent technique was used for 30 years after that and was successful in detecting ACA in 61% of patients with autoimmune AD of varying duration and in about 90% of those with newly-diagnosed autoimmune AD, but in less than 2% of those with tuberculosis-related AD, according to Betterle.