Disponible en ligne sur
ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com
Annales d'Endocrinologie xxx (2017) xxx–xxx
Annales d'Endocrinologie
Annals of Endocrinology

Klotz Communications 2018: Cortisol and all its disorders

Autoimmune Addison's disease – An update on pathogenesis

La maladie d'Addison auto-immune – une mise à jour sur la pathogenèse

Alexander Hellesen [a,b], Eirik Bratland [a,b], Eystein S. Husebye [a,b,c,d,*]

[a] *Department of Clinical Science, University of Bergen, 5021 Bergen, Norway*
[b] *K.G. Jebsen Senter for Autoimmune Sykdommer, University of Bergen, 5021 Bergen, Norway*
[c] *Department of Medicine, Haukeland University Hospital, 5021 Bergen, Norway*
[d] *Department of Medicine (Solna), Karolinska Institutet, 17176 Stockholm, Sweden*

Abstract

Autoimmunity against the adrenal cortex is the leading cause of Addison's disease in industrialized countries, with prevalence estimates ranging from 93–220 per million in Europe. The immune-mediated attack on adrenocortical cells cripples their ability to synthesize vital steroid hormones and necessitates life-long hormone replacement therapy. The autoimmune disease etiology is multifactorial involving variants in immune genes and environmental factors. Recently, we have come to appreciate that the adrenocortical cell itself is an active player in the autoimmune process. Here we summarize the complex interplay between the immune system and the adrenal cortex and highlight unanswered questions and gaps in our current understanding of the disease.
© 2018 Elsevier Masson SAS. All rights reserved.

Keywords: Addison's disease; Autoimmunity; Pathogenesis; Adrenalitis

Résumé

L'auto-immunité contre le cortex surrénalien est la principale cause de la maladie d'Addison dans les pays industrialisés, avec des estimations de prévalence allant de 93 à 220 cas par million d'habitants en Europe. L'attaque immunitaire des cellules corticosurrénales affaiblit leur capacité à synthétiser des hormones stéroïdes vitales et nécessite un traitement hormonal substitutif définitif. L'étiologie de la maladie auto-immune est multifactorielle impliquant des polymorphismes dans les gènes immunitaires et des facteurs environnementaux. Récemment, nous avons appris que la cellule corticosurrénale elle-même joue un rôle actif dans le processus auto-immun. Nous résumons ici l'interaction complexe entre le système immunitaire et le cortex surrénalien et soulignons les questions et les lacunes sans réponse dans notre compréhension actuelle de la maladie d'Addison.
© 2018 Elsevier Masson SAS. Tous droits réservés.

Mots clés : Maladie d'Addison ; Glande surrénale ; Auto-immunité

1. Introduction

Addison's disease (AAD), or primary adrenocortical insufficiency, is characterized by inability of the adrenal cortex to produce sufficient amounts of glucocorticoids and mineralocorticoids. The disease often manifests itself between the 2nd and 4th decade of life and affects women more often than men [1–3]. Patients may present with several diffuse symptoms such as fatigue, nausea, dizziness and weight loss, but can often be identified by specific signs like salt-craving and, especially, hyperpigmentation of the skin and mucosal surfaces [1,4]. The latter is caused by increased stimulation of melanocortin receptors in the skin by ACTH and pro-opiomelanocortin (the precursor for ACTH), that builds up in patients due to lack of cortisol-mediated feedback inhibition of the HPA-axis [5]. Consequently, elevated plasma ACTH as well as low serum cortisol levels serves as diagnostic criteria for AAD.

The current recommended treatment regimen consists of hormone replacement therapy in the form of hydrocortisone

* Corresponding author. Department of Clinical Science and University of Bergen, 5021 Bergen, Norway.
E-mail address: Eystein.Husebye@uib.no (E.S. Husebye).
https://doi.org/10.1016/j.ando.2018.03.008
0003-4266/© 2018 Elsevier Masson SAS. All rights reserved.

Please cite this article in press as: Hellesen A, et al. Autoimmune Addison's disease – An update on pathogenesis. Ann Endocrinol (Paris) (2017), https://doi.org/10.1016/j.ando.2018.03.008

(glucocorticoid replacement) and fludrocortisone (mineralocorticoid replacement) [6]. If left untreated, a stressful event (e.g. watching a high profile premier league football match [7]) may eventually precipitate acute adrenal insufficiency (adrenal crisis) – a potentially life-threatening condition caused by critical hormone-deficiency [8].

Although tuberculosis was the predominant cause of AAD earlier [9], autoimmunity is now responsible for most of the cases in developed countries [1,4]. The identification of steroid cytochrome P450 21-hydroxylase (21OH) of the adrenal cortex as a major autoantigen has led to routine use of 21OH autoantibody assays in determining the disease aetiology [6,10]. Among Norwegian patients, 86% was found positive for such autoantibodies [1], and similar numbers have been reported in other populations [2,4,11]. Autoantibodies against the adrenal cortex are often detectable prior to the development of overt disease [12] and in as much as 95% of patients at the time of diagnosis [13]. Less than 0.5% of the general population harbor anti-21OH antibodies [14] and these "antibody biomarkers" are therefore highly specific for autoimmune AAD. In a prospective study, the cumulative risk of developing AAD in antibody-positive individuals was estimated to about 30% [12]. Although AAD may occur in isolation, more than half of the patients suffer from additional autoimmune diseases. Autoimmune thyroid disease (AITD; hypo- or hyperthyroidism) is the most frequent comorbidity, followed by diseases like type 1 diabetes (T1D), chronic atrophic gastritis and vitiligo [2,11,15,16]. The coexistence of at least two out of the three diseases AAD, AITD and T1D is commonly referred to as autoimmune polyendocrine syndrome type 2 (APS-2) [17]. AAD is also a major disease component of the monogenic syndrome APS-1 [18,19], in which the presence of two out of the following three manifestations is diagnostic: AAD, chronic mucocutaneous candidiasis and hypoparathyroidisim. While the two syndromes share several features such as the presence of serum 21OH autoantibodies [4] and immune infiltration of the adrenal cortex (when AAD is involved) [20,21], the genetic background of APS-1 differs from APS-2 as the former is caused by mutations in the autoimmune regulator (AIRE) gene while APS-2 (including isolated AAD) is a polygenic disorder. Also, APS-1 is more rare than APS-2, with an estimated prevalence of 1:90,000 in Norway [22].

2. Genetic susceptibility

In agreement with most other organ-specific autoimmune disorders, the strongest genetic associations to AAD are found within certain HLA class II alleles. Significant risk has been confirmed in the presence of HLA DR3/DQ2 (DRB1*0301-DQA1*0501-DQB1*0201) and DR4/DQ8 (DRB1*0404-DQA1*0301-DQB1*0302) haplotypes, and especially the compound heterozygote combination (odds ratio = 32) [1,23,24]. Also, in a study of families with multiple affected individuals, increased risk for AAD was found to be associated with the HLA DR3-B8 haplotype [25]. The importance of these alleles has been further reinforced by studies on T cell responses in AAD [25–28]. Within the HLA locus, a connection has also been made to the MHC-class I chain-related gene A (MICA) [29], which encodes a ligand for the activating NK and T cell receptor NKG2D. Homozygosity for the MICA5.1 allelic variant was associated with increased frequency of progression to AAD in 21OH autoantibody-positive individuals bearing the high-risk genotype (DR3/DQ2-DR4/DQ8) [30].

Table 1
Genes outside the MHC complex associated with autoimmune Addison's disease.

Gene	Function	References
CTLA-4	Inhibits T cell activation	[32,96]
PD-L1	Inhibits T cell activation	[97]
PTPN22	Regulates T cell responses to weak peptide agonists; promotes TLR-induced type I IFN production in myeloid cells	[34,98]
NALP1	Inflammasome activation	[99,100]
STAT4	Involved in TH1 and TH17 differentiation	[101]
CIITA	Regulator of MHC class II transcription	[102,103]
BACH2	Regulates B and T cell differentiation	[23,37]
FCRL3	Regulates signalling pathways in lymphocytes	[104]
GPR174	Involved in suppression of IL2 production in T cells	[105]
GATA3	Transcription factor that acts on T cell differentiation	[101]
NFATC1	Involved in gene transcription in activated T cells and a major target of cyclosporine	[106]
CLEC16A	Modulates autophagy and T cell selection in the thymus	[103]
CYP27B1	Enzyme involved in vitamin D metabolism	[107–109]
VDR	Vitamin D receptor	[110]

Several studies have reported SNPs in immune-related genes that confer increased risk for AAD. Most of these genes encode proteins that are active in regulating T and B cell activation and differentiation (Table 1, see also [31] for a review of the subject), underlining the importance of these cell types in the pathobiology of AAD. A recent meta-analysis of European AAD cohorts strengthened the link to CTLA-4 [32], hypothesizing that the associated genetic variants may impair CTLA-4 function and thereby lower the threshold for T cell activation as suggested in AITD [33]. Another interesting association is the 1858T-allele of PTPN22 [34] as recent publications implicate PTPN22 in distinct processes that may be of particular importance to autoimmunity; regulation of T cell responses to weak self-peptide agonists [35] and promotion of type I IFN production in myeloid cells following TLR stimulation [36]. Recently, a comprehensive exome sequencing effort of patients from the Swedish Addison Registry revealed *BACH2* as a major risk locus for AAD [23], corroborating another recent finding that a SNP in BACH2 is associated with increased risk of developing AAD in the UK and in Norway [37]. BACH2 is a transcription factor that is essential for T and B cell development and variants in the BACH2 gene has been associated with increased risk of developing a wide range of autoimmune diseases, including T1D, AITD and celiac disease [38–40].

Please cite this article in press as: Hellesen A, et al. Autoimmune Addison's disease – An update on pathogenesis. Ann Endocrinol (Paris) (2017), https://doi.org/10.1016/j.ando.2018.03.008

Download English Version:

https://daneshyari.com/en/article/8720518

Download Persian Version:

https://daneshyari.com/article/8720518

Daneshyari.com