Autoimmunity Reviews 13 (2014) 408–411

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Diagnosis and classification of Addison's disease (autoimmune adrenalitis)

Rodrigo Antonio Brandão Neto [a], Jozélio Freire de Carvalho [b,*]

[a] Emergency Division, Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
[b] Rheumatology Division, Aliança Medical Center, Salvador, Bahia, Brazil

ARTICLE INFO

Article history:
Accepted 13 November 2013
Available online 11 January 2014

ABSTRACT

Autoimmune adrenalitis, or autoimmune Addison disease (AAD), is the most prevalent cause of primary adrenal insufficiency in the developed world. AAD is rare and can easily be misdiagnosed as other conditions. The diagnosis depends on demonstrating inappropriately low cortisol production and the presence of high titers of adrenal cortex autoantibodies (ACAs), along with excluding other causes of adrenal failure using other tests as necessary. The treatment corticosteroid replacement, and the prognosis following the treatment is the same as the normal population. Spontaneous recovery of adrenal function has been described but is rare.

Contents

1. Introduction

The adrenal gland was first described in 1552 by Bartolomeu Estaquio as the "Glandulae renis incumbents", in Opuscula Anatômica [1], although its function remained a mystery for centuries. However, the mystery began to be solved in 1885, when Thomas Addison described the clinical features of 11 patients with primary adrenal insufficiency [2]. In 1949, the synthesis of cortisone allowed the treatment of this condition [3].

The role of autoimmunity in primary adrenal disease became clear after a 1957 study by Anderson and colleagues identified adrenal cortex autoantibodies (ACAs) in the serum of patients with Addison's disease [4]; these ACAs were of the immunoglobulin subclasses IgG1, IgG2 and IgG4 and are found in 60–81% of patients with chronic adrenal autoimmune etiology [5]. In 1992, the enzyme steroidogenic 21-hydroxylase (21OH) was identified as the major antigen recognized by ACAs [6].

2. Epidemiology

There are two types of adrenal insufficiency: primary and secondary. Chronic primary adrenal insufficiency has a prevalence of 93–140 per million people and an incidence of 4.7–6.2 per million people in white populations [7–11]. The incidence of secondary adrenal insufficiency is much higher than that of primary insufficiency, but the former does

* Corresponding author at: Alameda Franca 435 Apto 21, São Paulo, SP 01422000, Brazil.
E-mail address: rodneto@gmail.com (J.F. Carvalho).

1568-9972/$ – see front matter
http://dx.doi.org/10.1016/j.autrev.2014.01.025

not fall within the scope of this article. It is likely that the real prevalence of the disease is unknown due to misdiagnosis; a survey of patients with Addison's disease by the National Adrenal Disease Foundation reported that 60% had enlisted the services of two or more physicians before receiving a correct diagnosis [12]. Autoimmune adrenalitis (AAD) is the main cause of adrenal insufficiency after the introduction of tuberculosis therapy and is responsible for 68–94% of the cases in European and North American reports [5,13–16]. AAD is isolated in 40% of cases and is part of an autoimmune polyendocrine syndrome in the remaining 60% [11].

During the first two decades of life, isolated AAD is predominantly observed in males (70%); however, after the third decade of life, there is a substantial female preponderance (81%) [17]. Among patients with AAD as part of one of the polyglandular autoimmune syndromes, there is also a female predominance (70%) [17].

2.1. Pathogenesis of AAD

Humoral and cellular immunity play roles in AAD pathogenesis. Environmental triggers, such as viral infections, drugs, smoking, food and stress, could play roles in genetically predisposed individuals [5]. With regard to genetic susceptibility, associations with HLA B8, DR3 and DR4 alleles have been observed, except in cases of polyglandular syndromes, in which no specific HLA associations have been identified [18].

The main characteristic of AAD is the presence of serum antibodies against the steroidogenic enzymes, with antibodies against 21OH being the most prevalent [19–21]. The role of ACAs in the pathogenesis of AAD has not been established; in fact, it appears that the destruction of adrenocortical cells mediated by T lymphocytes is a predominant feature and that the production of antibodies against 21OH is secondary to the release of peptides by that destruction and the production of the antibodies related to it. Therefore, antibodies against 21OH are most likely more accurately thought of as serological markers of the autoimmune process rather than the cause of the disease itself [22]. As previously mentioned, these antibodies are of the IgG1 or IgG2a subclass [23,24], suggesting that T helper (Th) cells are involved in the destruction of the adrenal cortex in patients with autoimmune Addison's disease [25]. With respect to cellular immunity, decreased suppressor T-cell function and an increased number of circulating Ia-positive T cells have been described in AAD patients [26].

3. Pathological features

The adrenal glands are invariably small in AAD-affected patients. Histopathology reveals a widespread mononuclear cell infiltrate, containing lymphocytes, plasma cells and macrophages, during the active phase. The normal three-layer histological structure is not pronounced, and pleomorphism and necrosis of adrenocortical cells can be observed [27].

4. Clinical findings

Addison's disease is the final result of AAD; the initial phase is subclinical, and after at least 90% of the adrenal gland has been destroyed, symptoms of adrenal failure appear [28]. Acute adrenal insufficiency is a life-threatening disease that involves severe hypotension or hypovolemia, acute abdominal pain, nausea and vomiting [11]. Other symptoms include anorexia, fever, weakness, fatigue, lethargy and confusion. Most patients have predisposing factors that acutely increase their need for corticosteroids, such as trauma, surgery and infections. Shock that is unresponsive to volume and vasoconstrictor agents is a typical finding. During chronic disease, the main finding is fatigue, and patients also present weakness, lack of stamina and weight loss. Gastrointestinal problems are also frequent and include nausea and abdominal pain, possibly related to a loss of gut mobility [29]. Dizziness, irritability and postural hypotension are also frequent complaints; patients may survive without a diagnosis for many years, until a minor infection leads to cardiovascular collapse [30]. Hyperpigmentation and salt-craving are highly specific to primary adrenal insufficiency.

The onset of the disease can be insidious, taking years to diagnose or to lead to the development of an acute crisis following an intercurrent illness [31,32]. The major manifestations of the disease and their frequency are described in Table 1.

5. AAD and autoimmune polyendocrine syndromes (APS)

AAD is part of an autoimmune polyendocrine syndrome (APS) in 60% of patients [11,16,33]. AAD is a major part of APS-1 and APS-2.

APS-1, also termed autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED), is identified in up to 15% of patients with AAD [11]; this syndrome is defined by the presence of adrenal insufficiency, hyperparathyroidism, and chronic mucocutaneous candidiasis, with onset often occurring during childhood [16,34], and it is associated with autoimmune regulator (AIRE) gene mutations [11,35,36]. APS-2 consists of adrenal insufficiency and autoimmune thyroid disease (Schmidt syndrome) or type 1 diabetes mellitus (Carpenter syndrome), and its manifestations include primary gonadal failure, type 1 diabetes mellitus and other autoimmune diseases, such as vitiligo and autoimmune atrophic gastritis, among others. APS-2 is also strongly associated with HLA-DR3 and CTLA-4 [11,16]. AAD also occurs with other autoimmune disorders but without autoimmune thyroid disease in APS-4; however, this condition is far less frequent than are APS-1 and APS-2.

6. Laboratory and imaging findings

Hyponatremia is described in 85–90% of AAD patients, but it is usually less pronounced than in secondary adrenal failure [30,31]. Hyperkalemia is reported in approximately 65% of AAD patients [30]. The adrenal glands are usually small, in contrast to the larger volumes observed in tuberculosis and neoplasias; consequently, in a patient with adrenal insufficiency with small non-calcified adrenal glands in abdominal tomography, AAD is likely the cause [37,38].

Table 2 summarizes the laboratory findings in AAD. The diagnosis depends upon the demonstration of inappropriately low cortisol production. Cortisol levels of less than 3 μg/dl when measured in the morning (between 8 and 9 am) are strongly suggestive of adrenal insufficiency [30,31,39]. Conversely, levels higher than 19 μg/dl exclude this diagnosis. Levels between 3 and 19 μg/dl require additional tests. Alternatively, a short adrenocorticotropic hormone (ACTH) stimulation test can be performed using an intravenous dose of 250 μg synthetic ACTH (cosyntropin). If there is an increase in the serum cortisol level 30 or 60 min after this injection to a peak less than 18 μg/dl (500 nmol/l), a diagnosis of adrenal insufficiency can be made [40]. The use of a low-dose ACTH stimulation test or an insulin-induced hypoglycemia test is usually unnecessary and restricted to situations in which secondary adrenal insufficiency is suspected.

Table 1
Clinical manifestations of Addison's disease.

Symptoms	Frequency
Weakness and fatigue	74–100% [5,30]
Anorexia	61–100% [5,30]
Weight loss	78–100% [30]
Hypotension and tachycardia	88–94% [30]
Abdominal pain	31% [30]
Nausea, vomiting	75–86% [30]
Diarrhea	6–16% [5,30]
Salt-craving	9–16% [5,30]
Depression	20–40% [30]
Postural symptoms	12–15% [32]
Skin or mucosal hyperpigmentation	80–94% [5,30]
Amenorrhea or reduced libido	25–45% [5,31]