Autoimmune Addison Disease or Autoimmune Adrenalitis

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Abstract
Autoimmune adrenalitis is the most common cause of adrenal failure in developed countries, accounting for about 70% of the cases, characterized by primary adrenal failure and circulating antibodies against enzymes of adrenal cortex. The clinical manifestations are similar to other causes of Addison disease and adrenal glands are usually small and atrophic. This chapter discusses the clinical manifestations, pathology, diagnosis, and treatment of this condition and proposes a diagnostic criteria for the disease.

Keywords
Addison disease · adrenal · adrenal insufficiency · diagnostic criteria · adrenalitis

Epidemiology
Addison disease is a rare disorder; however, it is more common now than how it was 30 years ago because its prevalence in the general population has increased three times since 1970 (1). Male patients are affected with isolated AAD predominately (70%) during the first two decades of life; there is no predominance during the third decade, and thereafter a female preponderance (81%). The female gender is also more frequently affected, when AAD is part of the clinical picture of polyglandular autoimmune syndrome (70%) (2). Primary adrenal insufficiency is clinically evident in 1 in 8000 individuals in Western countries (3, 4) and AAD is the most common cause in these countries, accounting for 68–94% of cases in different studies (1), but the real prevalence of the disease is unknown. A survey of patients with Addison’s disease and who are members of the National Adrenal Disease Foundation revealed that 60% had sought the medical attention of two or more physicians before the correct diagnosis was ever made (5). No statistics is available on the number of undiagnosed patients succumbing to adrenal insufficiency.

Pathogenesis
Humoral and cellular immunities play a role in the pathogenesis of AAD. The role of autoantibodies is described in a later section. On cellular immunity, decreased suppressor T-cell function and increased number of circulating Ia-positive T cells have been described in AAD patients (6). With regard to genetic susceptibility, an association with HLA B8, DR3, and DR4 alleles has been observed, except in cases of polyglandular syndrome, in which no specific HLA association has been found (7).

Clinical Manifestations
The symptoms and signs of adrenal insufficiency depend upon the rate and extent of loss of adrenal function. In the acute scenario, nausea, vomiting, anorexia, abdominal pain, fever, weakness, fatigue, lethargy, confusion, and coma may appear. Shock not responsive to volume and vasoconstrictor agents is a typical finding. In the case of chronic disease, the usual complaints center on weakness, fatigue, and weight loss. There are frequent gastrointestinal problems such as nausea and severe abdominal pain, possibly related to loss of gut motility. Dizziness is also a frequent complaint and appears when patients are standing; patients may present with darkening of the skin, hair, and nails, but the symptoms could be so vague that the patient may survive without diagnosis for many years until a minor infection leads to cardiovascular collapse (8). The major findings of the disease are described in Table 47.1.

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**Pathological Features**

The adrenal glands are usually small, in contrast to larger volumes observed in tuberculosis or neoplasias. Histopathology reveals a widespread mononuclear cell infiltrate with lymphocytes, plasma cells, and macrophages during active phase. The normal three-layer histological structure is not more distinguishable, and there is peliomorphism and necrosis of the adrenocortical cells. Subsequently, fibrous tissue can replace the cortex. Adrenal insufficiency manifestations appear only after at least 90% of the cortex has been destroyed (9).

**Laboratory Features**

Table 47.2 summarizes the laboratory findings in AAD. Levels of cortisol, measured between 8 and 9 am, <3 μg/dL confirm the diagnosis of adrenal insufficiency. On the contrary, levels >19 μg/dL exclude this diagnosis. Levels between 3 and 19 μg/dL require additional tests. Alternatively, a short ACTH stimulation test can be performed using intravenous 250 μg of synthetic ACTH. If after 30 or 60 min of this injection there is an increase in serum cortisol level to a peak <18 μg/dL (500 nmol/L), the diagnosis of adrenal insufficiency is established (Table 47.3).

**Autoantibodies**

For many years, the best marker for identifying AAD has been high titers of cortex adrenal cortex autoantibodies (ACAs), detected by indirect immunofluorescence on cryostatic sections of adrenal glands (1). These antibodies bind all three zones of the adrenal cortex. Low titers of ACA have been described in unequivocal post tuberculosis adrenalitis. More recently, the identification of the enzyme steroid-21-hydroxylase as the antigen allowed the development of highly sensitive and specific radio-binding assays for steroid-21-hydroxylase (CYP21A2 or P450c21) autoantibodies detection (10) The antigen targets are the steroidogenic enzymes: P450scc (CYP11A1, side-chain cleavage enzyme), P450c17 (CYP17, 17-alpha-hydroxylase), and P450c21 (CYP21A2, 21-hydroxylase). These antibodies may be present in 80% of the cases (1). Anti-adrenal antibodies are more common in women and in patients with autoimmune disorders who have these autoantibodies develop adrenal insufficiency at a rate of up to 19% per year (11). In fact, the presence of ACA in polyglandular autoimmune syndrome type 1 patients has a predictive value for the development of adrenal insufficiency of 92% in this population.

**Diagnostic Criteria**

First, it is necessary to diagnose adrenal insufficiency (Table 47.3). The second step is to define the autoimmune nature of this process; however, there are no diagnostic criteria available. We therefore suggest in this chapter some elements that can lead to AAD diagnosis. The main point in the differential diagnosis is to exclude secondary conditions that can cause adrenal insufficiency, such as tuberculosis, HIV, drugs, and genetic disorders. After excluding these conditions, it is important to have an image of adrenal glands; the finding of an enlarged gland makes the autoimmune process less probable. On the contrary, the presence of autoantibodies to adrenal tissue or against steroid enzymes practically confirms the diagnosis of autoimmune adrenal insufficiency. Alternatively, in the absence of these antibodies and with concomitant autoimmune conditions, the probable diagnosis can also be supported (Table 47.3).