The General Practice Guide to Autoimmune Diseases

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Pabst Science Publishers
Lengerich, Berlin, Bremen, Miami,
Riga, Viernheim, Wien, Zagreb

Bibliographic information published by Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at <http://dnb.ddb.de>.

http://www.pabst-publishers.de

Printing: MercedesDruck, Berlin
Typesetting: Hilmar Schlegel, Berlin
Cover: Agentur für zeitgemäße Kommunikation Kaner Thompson
www.kanerthompson.de

ISBN 978-3-89967-770-6

Autoimmune Addison's disease or autoimmune adrenalitis

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1 Introduction

Autoimmune adrenalitis (AAD) is currently the most common cause of primary adrenal insufficiency or Addison's disease [1]. It is characterized by deficient production of glucocorticoids and/or mineralocorticoids by the adrenals due to an autoimmune process. Addison's disease is a rare disorder, however it is more common than 30 years ago; its prevalence in the general population having increased three fold since 1970 [1]. Primary adrenal insufficiency is clinically evident in 1 in 8 000 individuals in Western countries [3, 4] and AAD is the most common cause in these territories, accounting for 68–94 % of cases in the different studies [2]. The symptoms and signs of adrenal insufficiency depend upon the rate and extent of loss of adrenal function (Table 1).

2 Diagnostic measurements for experts

The first step is the confirmation of the clinical diagnosis of primary adrenal insufficiency demonstrating [2]:

1. Low basal cortisol and high ACTH secretion [basal cortisol < 3 μg/dL (83 nmol/L) and/or ACTH > 100 pg/mL (22 pmol/L), at 8:00 to 9:00 am], or
2. A rise in serum cortisol level up to 18 mcg/dL (500 nmol/L), 30 or 60 minutes after injecting 250 μg IV of ACTH

The second step is to define the autoimmune nature of this process; however there are no diagnostic criteria available. 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 the adrenal glands; the finding of an enlarged gland makes the autoimmune process less probable. On the other hand, the presence of autoantibodies to adrenal tissue or against steroid enzymes practically confirms

Table 1. Clinical manifestations of Addison's disease.

Symptoms	Frequency
Weakness and fatigue	95–100 %
Anorexia	95–100 %
Weight Loss	95–100 %
Dehydration	80 %
Hypotension and tachycardia	88–94 %
Abdominal pain or cramps	31 %
Nausea, vomiting	75–86 %
Diarrhoea	16 %
Salt craving	16 %
Postural symptoms	15 %
Skin or mucosal hyperpigmentation	90–94 %
Lethargy	90 %
Amenorrhoea and reduced libido	(frequency not reported in most series)

the diagnosis of autoimmune adrenal insufficiency. In the absence of these antibodies but with concomitant autoimmune conditions, the probable diagnosis of AAD can also be supported. We have previously suggested some elements that can lead to AAD diagnosis (Table 2) [2].

3 Requirements for family practitioners

Signs and symptoms of adrenal insufficiency depend on the extent and rapidity of loss of adrenal function, mineralocorticoid production, and the degree of stress. The onset of adrenal insufficiency is often very gradual and it may go undetected until an illness or other stress precipitates adrenal crisis. Patients may have dehydration, hypotension, or shock disproportionate to the severity of the current illness; abdominal pain; nausea and vomiting; weight loss and anorexia; hypoglycaemia; fever; hyponatraemia, hyperkalaemia, azotaemia, hypercalcaemia, or eosinophilia; hyperpigmentation or vitiligo. Definite diagnosis of primary Addison's disease is determined by cortisol and ACTH measurements that show inappropriately low cortisol secretion with high ACTH levels. Secondary conditions such as tuberculosis or tumour should be excluded by adrenal imaging techniques. The presence of autoantibodies against adrenal components confirms the autoimmune nature, and is seen in 80 % of the cases.

Table 2. Proposed diagnostic criteria for Autoimmune Addison's disease.

1. Basal cortisol < 3 μ g/dL (83 nmol/L) and/or ACTH > 100 pg/mL (22 pmol/L), at 8:00 to 9:00 am

   or

   Short ACTH stimulation test with 250 μg IV leading a rise in serum cortisol level after 30 or 60 minutes to a peak of at least 18 mcg/dL (500 nmol/L).
2. Normal or reduced adrenal gland volume on computed tomography (CT) and MRI and absence of calcifications on abdominal X-ray or CT.
3. Anti-cortex adrenal antibodies or high titres of anti-21-hydroxylase antibodies.
4. Exclusion of other causes of primary adrenal insufficiency: genetic (clinical signs or symptoms: achalasia, alacrimia, deafness, or hypogonadotropic hypogonadism in males or genotyping); adrenoleukodystrophy (levels of very long chain fatty acids within normal range); infectious diseases (tuberculosis, paracoccidiomycosis, histoplasmosis, HIV, CMV); drugs (mitotane, ketoconazoles, rifampin, etc); adrenal haemorrhage or thrombosis; neoplasias; infiltrative (sarcoidosis, amyloidosis, haemochromatosis).
5. Other(s) concomitant auto-immune condition(s) (Hashimoto's thyroiditis, pernicious anaemia, rheumatological autoimmune disease, autoimmune haemocytopenia and others)

Definitive diagnosis 1, 2, 3 and 4;
Probable diagnosis 1, 2, 4 and 5

4 Follow up

Clinical observations

After corticosteroids therapy is initiated, a strikingly progressive improvement of the clinical pictures is observed. Hypertension, bradycardia, suppressed renin levels, and retardation in growth rate are clinical signs of over-treatment with mineralocorticoids.

Expectations

The survival of adequately diagnosed and treated patients is the same as for the normal population. Before the availability of steroid replacement, the survival rate was usually two years or less.

Blood tests

Serum potassium, glucose, and plasma renin activity should be monitored as part of treatment follow-up.

5 Management

The standard initial therapy is replacement with glucocorticoids. During an acute crisis, therapy should not be delayed for diagnostic studies or laboratory results. Hydrocortisone, 100 mg intravenously every 6 hours for 24 hours, should be given for all patients with strong clinical suspicions of AAD, together with physiologic saline (1 litre in the first hour is appropriate in most cases). After cardiovascular stabilization, the hydrocortisone dose should be reduced to 50 mg every 6 hours and subsequently tapered to oral maintenance in 4 to 5 days. In case of complications or persistence of the symptoms, maintain or increase the dose to 200 to 400 mg/day. The correction of the haemodynamic and metabolic disturbances with large volumes of intravenous saline and glucose is mandatory. Look for precipitating factors and particularly for infections.

Glucocorticoid chronic replacement is usually given in two to three doses, with a half to two thirds of the dose in the early morning to mimic the physiologic secretion pattern. Dosage is equivalent to the oral administration of 15–25 mg of hydrocortisone or 25–37.5 mg of cortisone acetate. Mineralocorticoid replacement is accomplished with fluorohydrocortisone (fluorinef, 0.05–0.2 mg daily).

Education is important and a personal card or bracelets/necklace carrying the diagnosis should be recommended.

In periods of stress, increasing cortisol dosage is strongly recommended for all patients. Patients undergoing surgical procedures also need to adjust the glucoccorticoid dose. For major surgery, administration of intravenous hydrocortisone 100 mg/m^2 per day is necessary for 24 h peri and postoperatively, before tapering the dosage over several days to a maintenance one [2]. Patients should also learn when and how to inject dexamethasone during emergencies.

6 Diagnostic tests

For many years, the best marker for the identification of AAD was high titres of cortex adrenal autoantibodies (ACA), detected by indirect immunofluorescence on cryostatic sections of adrenal glands [3]. These antibodies bind all three zones of the adrenal cortex. Low titres of ACA have been describe in unequivocal post tuberculosis adrenalitis. More recently, the identification of the enzyme steroid-21-hydroxylase as the relevant antigen has allowed the development of highly sensitive and specific radiobinding assays for steroid-21-hydroxylase (CYP21A2 or P450c21) autoantibodies detection [4]. 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 cases [3]. Anti-adrenal antibodies are more common in women. People with autoimmune disorders who carry these autoantibodies develop adrenal insufficiency at a rate of up to 19 % per year [5]. 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.

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