Mini Review

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The natural history of autoimmune Addison's disease with a non-classical presentation: a case report and review of literature

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Abstract: Autoimmune Addison's disease (AAD) is the most frequent cause of adrenocortical insufficiency. The natural history of AAD usually comprises five consecutive stages with the first stage characterized by the increase of plasma renin consistent with the impairment of *pars glomerulosa*, which is usually the first affected layer of the adrenal cortex. We describe a 19-year-old female with Hashimoto's thyroiditis (HT) who underwent an autoantibody screening due to having the personal and family history of other autoimmune diseases in the absence of relevant clinical manifestations. She was positive for adrenal cortex autoantibodies (ACA) and steroid 21-hydroxylase autoantibodies (21-OH Ab) at high titers. She had increased basal levels of ACTH with normal basal cortisol not responding to ACTH stimulation, reduced levels of dehydroepiandrosterone-sulfate but normal levels of orthostatic renin and aldosterone. This scenario was consistent with a subclinical AAD presenting with first impairments in *pars fasciculata* and *reticularis* and conserved *pars glomerulosa* function. Only subsequently, progressive deficiency in *pars glomerulosa* function has become evident. Review of the literature showed that there was only one case, reported to date, with a similar atypical natural history of AAD. The strategies for screening for ACA/21-OH Ab in patients with HT are discussed.

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Introduction and brief review of the literature

Primary adrenocortical insufficiency or Addison's disease (AD) is a rare, life-threatening condition with different aetiologies [1, 2]. The majority of cases are caused by autoimmune destruction of the adrenal cortex. Autoimmune Addison's disease (AAD) can present as an isolated condition or associated with other autoimmune diseases as part of an autoimmune polyglandular syndrome (APS) type 1, 2 or 4 [3]. Diagnosis of AAD, in the presence of adrenal cortical insufficiency, is based on the detection of adrenal cortex autoantibodies (ACA) and/or steroid 21-hydroxylase autoantibodies (21-OH Ab).

AAD is a chronic condition characterized by the natural history of five sequential distinct stages of impairment of adrenal cortex function which are detected in ACA/21-OH Ab-positive subjects using the ACTH test (Figure 1). The ACTH test evaluates blood levels of basal cortisol, ACTH, orthostatic renin, aldosterone and cortisol levels 60 min after ACTH stimulation [4]. Based on the ACTH test results, patients with normal adrenal function are at Stage 0 (potential AAD), whereas patients with increased plasma renin with normal or low levels of aldosterone and no other abnormal results are at Stage 1, which represents the start of adrenal cortex dysfunction. Stage 2 is characterized by the presence of high renin levels, low levels of aldosterone, normal basal ACTH and cortisol levels with low or no response of cortisol to ACTH stimulation. Stage 3 is characterized by the increase of basal ACTH with normal or low basal cortisol levels, and stage 4 by very high levels of ACTH with low levels of cortisol and the presence of clinical manifestations of AAD [2]. This suggests that in the

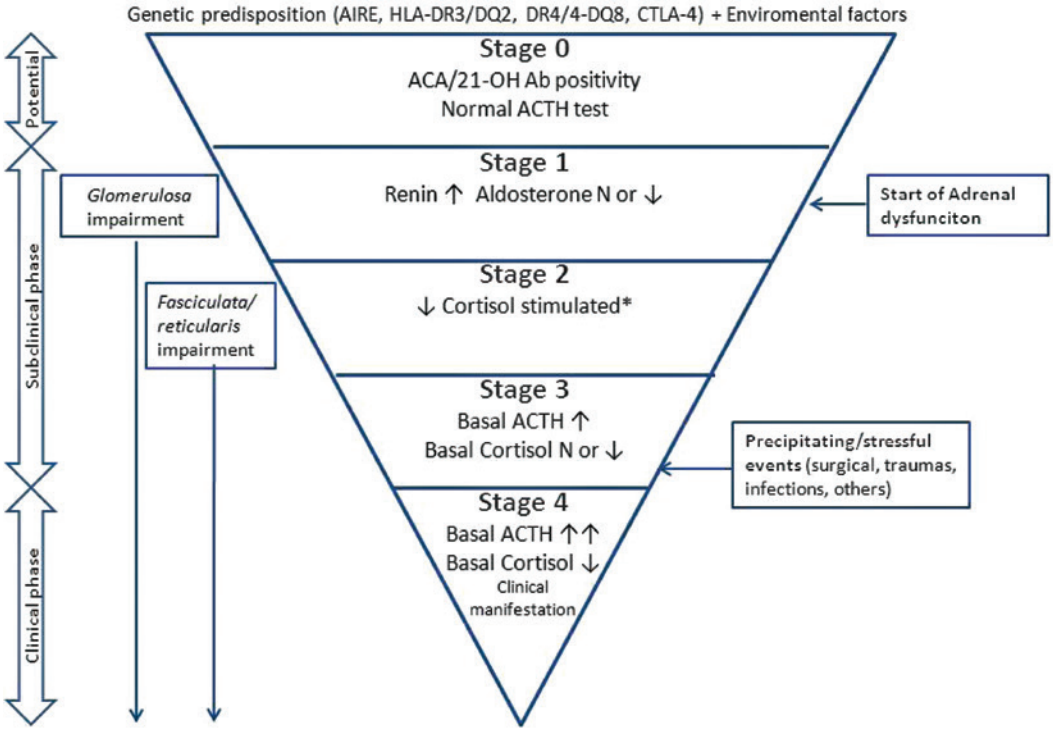

Figure 1: Classical natural history of autoimmune Addison's disease.
21-OH Ab, 21-hydroxylase autoantibodies; ACA, adrenal cortex autoantibodies; N, normal; *at 60 min after high dose (250 μg) ACTH test.

natural history of AAD, *pars glomerulosa*, responsible for production of aldosterone, is the first layer of the adrenal cortex affected and/or is the most sensitive to the autoimmune attack. The *fasciculata* and *reticularis* layers are most probably protected by the local production of cortisol and are affected only subsequently in the disease progression [2, 4–8]. In the reviewed literature, there were reports of 73 patients in total with ACA and/or 21-OH Ab positivity who had developed AAD of whom 66 demonstrated the typical progression through the stages 0–4 [5, 7, 9–15]. Only one patient presented with an atypical pattern of increased basal ACTH with normal basal orthostatic renin [15]. For the remaining six cases, the information on staging of AAD had not been available [15].

Case report

A 19-year-old female with Hashimoto's thyroiditis (HT) presented with hypothyroidism was under the care of our Endocrinology Unit and on levothyroxine she had normal TSH levels. The patient had personal history of juvenile idiopathic arthritis, which presented at the age of 4 years and resolved following treatment with glucocorticoids for several months. She has remained in remission since the age of 5 years. There was also a family history in the mother of vitiligo and HT. Due to the young age and the personal and family history, an autoantibody screening was carried out in the absence of relevant clinical manifestations. The screening revealed ACA positivity (titer >1/40; normal values <1/2) with an immunofluorescent pattern involving all the three layers of adrenal cortical (see Figure 2) and high titers of 21-OH Ab (>5000 IU/mL; normal values ≤1 IU/mL); the other autoantibodies to parietal cells, intrinsic factor, glutamic acid decarboxylase, islet cell and IgA-transglutaminase were found to be negative. In addition, autoantibodies to tryptophan hydroxylase, aromatic L-amino acid decarboxylase, p450 cytochrome side chain cleavage enzyme, steroid 17-α hydroxylase and interferon-omega were negative.

The patient, of Caucasian origin, presented a normal pigmentation of skin and mucosa, a normal arterial pressure (120/70 mmHg) either in supine or in orthostatic positions, a stable body weight, a body mass index of 19 kg/m^2 and complained only of a slight asthenia without other signs or symptoms of AAD. She did not take any medication other than levothyroxine. The laboratory tests for the assessment of the pituitary-adrenal axis showed that plasma levels of sodium and potassium, orthostatic aldosterone and renin and basal morning cortisol were normal;

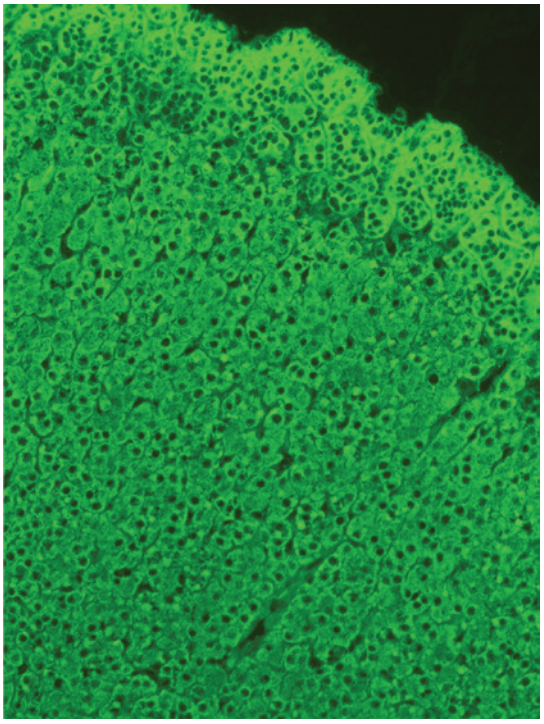

Figure 2: Immunofluorescent pattern produced by the serum of the patient: all the three layers of the monkey adrenal cortex are positive (250×).

however, there was an increase in morning basal ACTH without cortisol response to high dose of ACTH (250 μg) at 60 min (ACTH test) (Table 1). Further tests (12 days later) confirmed and completed investigations for the diagnosis of AAD (Table 1). The adrenal glands appeared normal on the magnetic resonance scans.

Based on these results, she was started the adrenal replacement therapy with a dual-release preparation of hydrocortisone (20 mg/day) in the morning upon awakening, and the patient and her relatives were instructed about managing therapy in the special circumstances and emergencies. After 1 and 3 months from the start of replacement therapy, the follow-up tests showed the increase of orthostatic renin and a decrease of orthostatic aldosterone to the low levels of the normal range. The morning basal ACTH and 24 h urinary free cortisol (24 h UFC) normalized on the corticosteroid substitutive therapy (Table 1). During follow-up, the blood pressure showed a tendency to orthostatic hypotension (100/70 mmHg), but patient's performance in daily life activities was good and electrolytes remained in the normal range. For this reason, fludrocortisone (0.025 mg) was started in the morning upon awakening. There was no clinical evidence of impaired gonadal function.

Ethical conduct of research: informed consent was obtained from the patient involved in this study.

Discussion

The association of HT with AAD configures an APS-2 (according to Betterle et al. [2]). The evaluation of patients with ACA/21-OH Ab-positivity in the absence of clinical manifestation is based on the high-dose ACTH test (250 μg), which helps to identify five progressive stages of adrenal cortex dysfunction (Figure 1). The increase of plasma renin levels with normal aldosterone levels has been reported in reviewed literature as the first marker of the progression towards AAD in 66 out of 73 patients [5, 7, 9–14]. Only one patient had an atypical pattern with an increase of basal ACTH in the presence of normal basal renin while for six patients information was not available [15]. We now report the second case of an atypical progression through the stages of adrenal dysfunction described

Table 1: The laboratory tests for the assessment of the pituitary-adrenal axis.

Parameters	Initial values	Values 12 days after	Values 1 month after start of therapy	Values 3 months after start of therapy
P-Natrium (n.v. 136–145 mmol/L)	142	140	140	141
P-Potassium (n.v. 3.4–4.5 mmol/L)	3.4	3.5	3.5	3.9
S-Orthostatic aldosterone (n.v. 70–1086 pmol/L)	240	n.t.	280	**87.6**
P-Orthostatic renin (n.v. 4.4–46.1 mIU/L)	34.2	n.t.	**55**	**60.2**
S-Morning basal cortisol (n.v. 138–690 nmol/L)	339	292	n.t.	n.t.
S-Cortisol stimulated[a] (n.v. >500 nmol/L)	**359**	n.t.	n.t.	n.t.
P-Morning ACTH (n.v. 10–50 ng/L)	**676**	**1090**	**231**	**117**
24 h UFC[b] (n.v. 16–168 nmol/24 h)	n.t.	**13**	129	n.t.
S-DHEA-S[c] (n.v. 0.9–11.7 μmol/L)	n.t.	**<0.4**	n.t.	n.t.
S-17 OH-progesterone (n.v. 1.5–6.4 nmol/L)	n.t.	3.5	n.t.	n.t.
S-Androstenedione (n.v. 1–11.50 nmol/L)	n.t.	1.73	n.t.	n.t.

[a]At 60 min after high dose (250 μg) ACTH test. [b]24 h urinary free cortisol. [c]Dehydroepiandrosterone-sulfate. n.t., no tested; P, plasma; S, serum. Bold indicates values that are out of the normal range.

to date. Our patient initially presented with raised basal ACTH with normal basal plasma cortisol levels and no response of cortisol to ACTH stimulation and with reduced levels of adrenal cortex androgens. These were signs of impairment of function in the *zona fasciculata* and *reticularis*, in the presence of preserved function of *zona glomerulosa*. Progressive *pars glomerulosa* deficiency developed only 1 month after the start of the therapy with hydrocortisone (Table 1). This case suggests that sometimes the autoimmune process may impair the *pars fasciculata* and *reticularis*, before affecting the *pars glomerulosa*.

In this case, adrenal dysfunction was diagnosed well before any clinical manifestations because of positive results for ACA/21-OH Ab tests. This raises the cost/benefit question of the screening for ACA/21-OH Ab in patients with thyroid autoimmune diseases (TAD).

Search of the literature showed that among 4353 adult patients with TAD tested for ACA by indirect immunofluorescence only 1% were found to be positive [12], and among 207 children with TAD none were found to be positive [13]. Recently, using a most sensitive and specific ELISA kit, 21-OH Ab were found to be positive in 1 (1.9%) out of 54 adult patients with HT and in none of the 50 adult patients with Graves' disease (GD), in 2/51 (3.9%) children with GD and in 3/69 (4.3%) children with HT [16]. The presence of such ACA is demanding periodical expensive functional adrenal cortical tests; however, only 1/3 of the patients with TAD and 21-OH Ab will developed clinical AAD during a median follow-up of 5 years [5]. By contrast, ACA are detectable from 6.5% to 20% of patients with premature ovarian failure (POF) [12, 17] and from 2.5% to 47.6% (mean value 18%) of patients with chronic hypoparathyroidism and/or chronic candidiasis [12, 13] with a very high cumulative risk (100%) of developing clinical AAD during a median follow-up of 5 years [5]. In view of the above, the screening for ACA/21-OH Ab is currently warranted in patients with POF or in patients with chronic hypoparathyroidism and/or chronic candidiasis while in patients with TAD alone its usefulness is still debated.

However, in our patient, testing for ACA/21-OH Ab was warranted because of presentation of two personal autoimmune diseases (HT and juvenile idiopathic arthritis) and a family history of vitiligo and HT. Consequently, testing for adrenal autoantibodies in the subset of patients with TAD and personal and/or family history of other autoimmune diseases and/or suspected for adrenal insufficiency could be warranted.

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