



Coexistence of 21 Hydroxylase Deficiency and Autoimmune Adrenalitis: A Case Report

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Abstract

21-Hydroxylase deficiency (21 OHD) is the most common cause of congenital adrenal hyperplasia (CAH). Despite its relative frequency, many aspects of this disease are understudied. The aim of our case report was to highlight the association between nonclassic CAH (NCCAH) and autoimmunity, and to encourage future research to explore the possible cause-and-effect relationship between CAH and tumorigenesis. Here, we report the case of a 41-year-old woman with a history of nonclassic 21 OHD, who demonstrated typical signs of acute adrenal insufficiency. As it is well known, this is an unusual presentation of NCCAH and therefore a panel of laboratory and radiological exams were conducted in order to determine the associated etiology of the adrenal insufficiency, which revealed to be autoimmune adrenalitis. Another striking particularity of our case is the coexistence of NCCAH and cutaneous T lymphoma in our patient, which to our knowledge has never been reported in literature. This case illustrates the need to scrutiny for the etiology of adrenocortical crisis in the setting of NCCAH. It also emphasizes the possible associations between NCCAH and autoimmunity in one hand and neoplasms on the other hand.

Keywords

- 21-hydroxylase deficiency
- autoimmunity
- Addison's disease
- cutaneous T-cell lymphomas
- neoplasms

Main Notes

1. Congenital adrenal hyperplasia could be associated with autoimmune diseases
2. Nonclassical congenital hyperplasia does not typically manifest as adrenal crisis
3. Congenital adrenal hyperplasia can be associated with lymphoma

Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disease. In 95% of the cases, CAH is the consequence of mutations in the cytochrome P450 family 21 subfamily A member 2 (CYP21A2) gene. There are two types of this disease:

the rarest type which is the classic CAH with severe enzyme deficiency resulting in two variants: the simple virilizing form and the salt wasting form; and the moderate enzyme deficiency corresponding to the nonclassical CAH (NCCAH).¹ The occurrence of acute adrenal insufficiency in patients with NCCAH is exceptional.² Here, we report the case of a woman

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with NCAH due to 21-hydroxylase deficiency (21 OHD) associated with Addison's disease and cutaneous T lymphoma.

Case Description

A 41-year-old woman presented at the emergency department in Sfax, Tunisia, with a symptomatology of fatigue, nausea, diarrhea, intractable vomiting, and painful urination, which she stated as having being present for the last 3 days.

She is the offspring of a nonconsanguineous couple. She had a family history of neonatal death of her three siblings due to dehydration, a mother with Hashimoto thyroiditis and hirsutism. Her sister also had hirsutism.

Our patient's medical history was relevant with 21-OHD diagnosed at the age of 21, treated with 20 mg of hydrocortisone: 10 mg on waking and 10 mg in the evening. During her previous admission in our department at the age of 21 years old, she had laboratory work showing an elevated serum levels of the cortisol precursor 17-hydroxyprogesterone (17-OHP), both basally: 36.31 nmol/L and after adrenal stimulation with cortrosyn: peak 160.38 nmol/L. Basal cortisol level was 493.7 nmol/L and peak after stimulation was 554.5 nmol/L. Basal sulfate dehydroepiandrosterone (SDHEA) 224 ng/mL was in the normal range. She had high testosterone level and adrenocorticotrophic hormone (ACTH) level (► **Table 1**).

Basal and after cortrosyn elevated 17-OHP, the nonelevated SDHEA, the absence of hypertension, and chronic adrenal insufficiency initially, makes other possible diagnosis of elevated 17-OHP less plausible such as a 3-beta-hydroxysteroid dehydrogenase deficiency, 11-beta-hydroxylase deficiency, and 17,20-lyase deficiency and therefore strongly suggest the 21-OHD.

The absence of ambiguous genitalia, peripubertal hirsutism, regular menses, preserved fertility, and moderate elevation of 17-OHP after cortrosyn stimulation (< 100 ng/mL) pointed toward a nonclassical 21-OHD. Unfortunately, genetic testing was not available in our hospital.

Moreover, she was admitted in our department at the age of 29 years, for an acute adrenal insufficiency. Her health history was also noticeable with cutaneous lymphoma in her 4th right finger cured at the age of 32 years with surgery and radiotherapy. Her puberty begun at the age of 11 years with spontaneous regular menses. She had three healthy children.

Upon admission she weighed 53 kg and her height was 1.49 m. She was normothermic. She had an accelerated heart rate 102 beats per minute, low blood pressure of 95/62 mm Hg, and eye circles, all reflecting a state of dehydration. Moreover, the patient exhibited signs of chronic adrenal insufficiency

such as weight loss, hyperpigmentation of her hands, and intolerance to Ramadan fasting for the last 3 years. She had moderate hirsutism with a Ferriman–Gallwey score of 18 (was 22 before laser treatment). She had nonambiguous female genitalia. Otherwise, a heterogeneous palpable thyroid was found following her examination.

These clinical and biological findings were compatible with an acute adrenal insufficiency, despite that the patient was on hydrocortisone. A prompt therapy with intravenous hydrocortisone, fluids, as well as antibiotics resulted in improvement of her symptoms.

The patient was discharged few days after admission with oral hydrocortisone 30 mg daily distributed as follows: 15 mg in the morning, 5 mg in the noon, and 10 mg in the night, aiming to suppress the hypothalamus–pituitary–adrenal axis and to provide a maintenance therapy. Since the increase of the dose, the patient showed a dramatic improvement over few weeks of her fatigue and her over all sense of well-being as well as the normalization of her 17-OHP levels.

A recent cortrosyn stimulation test was conducted 1 month after her recent adrenal crisis, revealing a basal cortisol level of 8.16 nmol/L, 8.8 nmol/L after 30 minutes of stimulation and 9.87 nmol/L after 60 minutes of stimulation, and hence confirming the diagnosis of chronic adrenal insufficiency. The elevated ACTH level indicated a primary adrenal insufficiency.

Although the diagnosis of adrenal insufficiency is certain, its etiology remained initially unclear. The patient did not stop her medications. She also did not take any drugs that could have precipitated an adrenal crisis (ketoconazole, fluconazole, etomidate, etc.). Since tuberculosis is one of the most common causes of adrenal insufficiency in our country, we conducted a thoracoabdominal computed tomography (CT) which did not reveal hyperplasia or hypoplasia of the adrenal glands and no adrenal calcifications, thus excluding this diagnosis. Given our patient's history of cutaneous lymphoma, adrenal lymphoma was a plausible diagnosis but the normal serum lactate dehydrogenase and the absence of adenomegaly and adrenal tumors on CT eliminated this diagnosis. Otherwise, the CT scan showed no suggestive signs of metastasis, infiltrative disease, hemorrhage, or infection of the adrenal glands.

Intriguingly, antiadrenal antibodies were positive and serum levels of 21-hydroxylase antibodies were above 100 U/mL (normal < 0.4 U/mL).

Dismissing the differential diagnosis, and regarding the strikingly highly positive antiadrenal and 21-hydroxylase

Table 1 Laboratory findings of our patient

	Patient results	Normal range
17 hydroxyprogesterone (nmol/L) basally	36.31	< 6
17 hydroxyprogesterone (ng/mL) after cortrosyn stimulation	160.38	< 30.26
Basal sulfate dehydroepiandrosterone (ng/mL)	224	10–330
Testosterone (ng/mL)	0.95	< 0.5
Adrenocorticotrophic hormone (pg/mL)	235.4	< 60

antibodies, and the familial history of autoimmune diseases, we can affirm that the adrenal insufficiency is attributable to an autoimmune adrenalitis (AA).

Discussion

Here, we report the case of an adrenal crisis due to a urinary infection occurring to a woman with a history of a NCCAH. Since adrenal crisis is not consistent with NCCAH, a panel of laboratory and imaging tests were conducted in order to pinpoint the associated etiology of the adrenal insufficiency.

Given the highly positive value of 21-hydroxylase antibodies, and since these antibodies are specific, the diagnosis of chronic autoimmune adrenal disease was made.³

Literature review revealed few cases that depicts the association between NCCAH and adrenal crisis. In fact, there was a similar case to our patient, describing a man with NCCAH who had an acute adrenal decompensation. Albeit the authors suggest that NCCAH may actually be responsible of his crisis,⁴ we do not agree with this hypothesis since they dismissed a major differential diagnosis which is AA based only on negative adrenal antibodies which lack sensitivity and specificity in comparison to 21-hydroxylase antibodies.

To our knowledge, four cases of CAH and autoimmune Addison's disease were reported in the literature,^{5–8} among them only two cases of 21-OHD and AA.^{6,7} The intriguing aspect of these associations are the revealing circumstances of AA. For instance, AA was suspected in the patient with 21-OHD on account of the vanishing 17-OHP levels despite the glucocorticoid tapering, considered given the patient's history of ulcerative colitis, suggesting autoimmune diseases and later confirmed using elevated 17-hydroxylase antibodies.⁶

Regarding the association between NCCAH and autoimmunity, according to a review by Falhammar et al, 21-OHD is associated with increased risk of autoimmune diseases, notably in those above 40 years and with simple virilizing form or the nonclassical phenotype.⁹ One of the postulated hypotheses explaining this rather rare association, is that a mutation of the CYP21A2 gene would result in a mutation of the 21-hydroxylase protein and therefore becomes a new antigen which might not be recognized by the immune system leading to an autoimmune reaction. Furthermore, concomitant mutations of the 4th component of complement and the CYP21 hydroxylase gene could easily occur due to the proximity of these two genes and lead to a low C4 which can reduce the clearance of immune complexes and thus causing autoimmune diseases along with NCCAH.⁹ These findings may be due to an incidental finding rather than a true association.

Another intriguing finding is the coexistence of cutaneous T cell lymphoma with a NCCAH which has never been, to our knowledge, previously reported in literature. However, NCCAH and B cell lymphoma were reported in one case report.¹⁰ As for the association between neoplasms and CAH, data is still scarce, and a pure coincidence could not be dismissed.

To summarize, our case sheds light on several aspects of NCCAH. First, it highlights the fact that adrenal crisis is not a

typical presentation of NCCAH and therefore its presence should prompt further investigation. Second, it suggests a possible dysregulation of the immune system in patients with NCCAH. Finally, it raises the possibility of association between NCCAH and the development of neoplasms, notably lymphomas.

Ethical Approval

Written informed consent was obtained from the patient.

Authors' Contributions

Conceptualization: D.B.S. and O.T. Data curation: F.H.K. and N.C. Formal analysis: M.E. and K.B. Methodology: M.M. and F.M. Project administration: F.M. Visualization: N.R., F.H.K., M.M.F., and M.A. Writing-original draft: O.T. Writing-review and editing: D.B.S., O.T., and H.F.

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Conflict of Interest

None declared.

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