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Case Report

A Rare Presentation of 17α-Hydroxylase/17,20-Lyase Deficiency in a Patient with non-Hodgkin's Lymphoma: A Case Report

Tekkeli N et al. Atypical Presentation of 17α Hydroxylase/17,20 Lyase Deficiency

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What is already known on this topic?
In 17α Hydroxylase/17,20 Lyase Deficiency, patients are usually diagnosed during adolescence period due to delayed puberty or amenorrhea. Due to excessive production of corticosterone, findings of adrenal failure are rare.

What does this study add?
Although clinical signs and symptoms of cortisol deficiency are not seen in 17α Hydroxylase/17,20 Lyase Deficiency, hyperpigmentation may be observed in stressful situations. Hypergonadotrotropic hypogonadism can be a sign of adrenal dysfunction.

Abstract
17α-hydroxylase/17,20-lyase deficiency (17OHD) is a rare form of congenital adrenal hyperplasia that causes decreased cortisol and sex steroid levels and leads to high production of adrenocorticotropic hormone (ACTH). Although affected patients have absolute cortisol deficiency, they do not show clinical signs of cortisol deficiency or hyperpigmentation. These patients most commonly present with delayed puberty and amenorrhea at late pubertal age. Impaired production of sex steroids leads to ambiguous or female external genitalia in affected 46, XY individuals. In this report, we describe a patient with 17OHD who presented with hyperpigmentation and hypergonodotropic hypogonadism while receiving chemotherapy.
Keywords: 17α-Hydroxylase deficiency, CYP17A1 gene, hyperpigmentation, hypergonadotrotropic hypogonadism, disorders/differences in sex development

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Introduction
Congenital adrenal hyperplasia (CAH) is a group of inherited autosomal recessive diseases caused by mutations in genes encoding steroidogenic enzymes required for cortisol, aldosterone, and adrenal sex steroid synthesis (1). 17α-hydroxylase/17,20-lyase deficiency (17OHD) is a rare form of congenital CAH and emerges as a result of mutations in the cytochrome P450 family (*CYP17A1*) gene on chromosome 10q24.3. The estimated prevalence is 1 in 50,000–100,000 (2,3). The enzyme 17α-hydroxylase/17,20-lyase (P450c17) is essential for the synthesis of cortisol and sex steroids. This enzyme has 17 α-hydroxylase and 17,20-lyase activities. The first reaction provides the transformation of pregnenolone and progesterone to 17α-hydroxypregnenolone (17-OHPreg) and 17α-hydroxyprogesterone (17-OHP) respectively. The second transforms 17α-hydroxysteroids to dehydroepiandrosterone and androstenedione. The absence of the enzyme causes decreased cortisol and sex steroid levels and leads to high production of adrenocorticotropic hormone (ACTH) that further drives the overproduction of 11-deoxycorticosterone (11-DOC) and corticosterone (4). High 11-DOC and corticosterone act as mineralocorticoids and lead to hypertension and hypokalemia. In addition, the impaired production of sex steroids leads to ambiguous or female external genitalia in affected 46, XY individuals, and normal genitalia in 46, XX individuals at birth, but no sexual development at the expected time of puberty. Affected patients most commonly present with hypertension, delayed puberty, and amenorrhea at late pubertal age (5). Although these patients also have absolute cortisol deficiency, they do not show clinical signs of cortisol deficiency due to the effect of corticosterone on the glucocorticoid receptor (6). However, in cases of severe stress, classic adrenal insufficiency findings may also occur in 17OHD. Here, we report the case of a 10 years and 6-month-old patient who was diagnosed with 17OHD while receiving treatment for non-Hodgkin's lymphoma without common findings of the condition.

Case Report
Ten-and-a-half-year-old girl with non-Hodgkin's lymphoma (NHL) was referred to pediatric endocrinology as the ovaries were not seen in the abdominal ultrasonography performed due to the abdominal pain. Eight months ago, she was diagnosed with pre-B-cell NHL and started to receive chemotherapy. The patient's history revealed that she had a mild hyperpigmentation in her skin, especially in the folds of the body when she was 4 years old and was evaluated as allergic. However, she used antiallergic medications, they were not effective. She reported increased darkening of the skin after the diagnosis and treatment of NHL. She was the third child of healthy parents. There was a first-cousin marriage between the parents. Anthropometric measures of patient were calculated by using reference values for Turkish children (7). In the physical examination, her weight was 43 kg (SDS: + 0.98), height was 150 cm (SDS: + 1.3) and body mass index was 19.11 kg/m^2 (SDS: + 0.57). Her blood pressure was 110/60 mmHg (95%: 121/78 mmHg), and she was prepubertal. The external genital structure was a typical female. There was hyperpigmentation in the skin folds (Figure 1), and liver was 7cm palpable in the subcostal region. Pelvic ultrasound and magnetic resonance imaging (MRI) revealed the absence of both ovaries and the uterus and atrophic gonads in the proximal right inguinal canal and the left lower abdominal quadrant. Hormonal tests showed hypergonadotropic hypogonadism **(Table 1)**. Plasma ACTH, anti-müllerian hormone (AMH), corticosterone, 11-DOC, and progesterone were found to be high, while cortisol, dehydroepiandrosterone sulfate (DHEAS), estradiol, total testosterone and 17-OH progesterone concentrations were low **(Table 1)**. Serum sodium and potassium levels were normal. Karyotype analysis was performed via G-banding following 72 h of cell culture from peripheral blood lymphocytes. The karyotype

was 46,XY. Blood samples from the patient and parents were collected using vacuum-EDTA tubes. DNA was isolated from the peripheral blood using QIAamp DNA Blood Mini Kit (Qiagen) following the manufacturer's protocol. Quantification of DNA concentration and purity assessment was carried out by spectrophotometric methods. Since the proband clinical features, biochemical and hormonal findings *CYP17A1* gene sequence analysis was performed with the preliminary diagnosis of 17OHD. All coding exons and exon-intron regions of the *CYP17A1* gene were sequenced using next-generation sequencing technology (Miseq, IlluminaInc., San Diego, CA, USA). To call variants, sequencing data were aligned with the human reference genome, hg19. According to genetic analysis a homozygous nonsense variation ((NM_000102): c.238C>T; p.Gln80*) was detected in the *CYP17A1* gene. The variation was not present in the ExAC, dbSNP, ClinVar, or HGMD databases, and was predicted to be likely pathogenic according to the ACMG criteria (PVS1, PM2). The segregation analysis revealed that the parents were both heterozygous for the *CYP17A1* c.238C>T(p.Gln80*) variant. Hydrocortisone treatment was initiated (10 mg/m^2/day in 3 doses). 24-hour blood pressure monitoring and echocardiography were normal. The patient was referred for psychiatric consultation. After the hydrocortisone treatment, the hyperpigmentation regressed during the follow-up. Sex steroid replacement was planned according to the gender chosen at the age of onset of puberty

Written informed consent was obtained from the family of the patient for publication of this report.

Discussion

In 17 OHD, patients are usually diagnosed during adolescence period due to delayed puberty or amenorrhea. The diagnosis of 17OHD before puberty is very rare unless there is a known case in the family (8). The main reason for presentation in pubertal ages is the absence of clinical signs of glucocorticoid deficiency and complete enzyme activity impairment in most patients, which results in normal female external genitalia in both sexes. Severe symptomatic hypertension in both 46, XX and 46, XY patients or inadequate virilization of external genitalia in 46, XY partial 17OHD may facilitate earlier diagnosis of the condition. (8,9) Our case is important because it was diagnosed at an early age without hypertension, delayed puberty or ambiguous genitalia.

In our case, the ovaries of the patient, who was being treated for non-Hodgkin's lymphoma, could not be seen in the abdominal USG performed due to abdominal pain. Subsequently, we diagnosed hypergonodotrophic hypogonadism. Evaluation of adrenal function study should be included in the etiological evaluation of hypergonadotropic hypogonadism in girls after excluding Turner Syndrome (10). The patient had no Turner syndrome stigmas. Chemotherapy is also among the causes of hypergonadotropic hypogonadism. However, since chemotherapy was started in our patient a short time ago, we did not consider chemotherapy in the etiology.

Biochemical detection of the case demonstrated that there were decreased concentrations of estradiol, total testosterone, DHEAS, androstenedione, and cortisol, as well as increased concentrations of progesterone, corticosterone, 11-DOC, and ACTH. The low levels of estradiol and testosterone led to female genitalia however the karyotype was 46, XY. Based on the clinical, biochemical, and molecular features, the patient was diagnosed with 17 OHD. In cases of 17OHD, steroid synthesis in both the adrenal glands and gonads is impaired (11). This leads to complete female external genitalia in both sexes when there is complete enzyme deficiency.

Since ACTH and melanocyte-stimulating hormone (MSH) are produced from proopiomelanocortin, hyperpigmentation may be observed in patients with 17OHD. However, ACTH concentration is not as high and hyperpigmentation is not as marked in patients with 17OHD compared with 21-hydroxylase (21OH), and 11β-hydroxylase (11βOH) deficiency. (8). Our patient also had mild hyperpigmentation since the age of 4. This color change was evaluated as an allergic reaction and she used allergy medications but they were ineffective. Nevertheless, the parents of our patient reported increased hyperpigmentation since the initiation of NHL chemotherapy which may suggest increased stress and compensatory increase in ACTH. Significant hyperpigmentation in the folds and darkening of the skin color decreased significantly approximately 2 weeks after hydrocortisone treatment started (Figure 2). In cases of unexpected hyperpigmentation of the skin, especially in the skin folds, adrenal functions should be checked.

Additionally, increased ACTH leads to a high amount of 11-DOC production. High levels of 11-DOC induce sodium and fluid retention and loss of potassium and hydrogen, and consequently hypertension, because of its potent mineralocorticoid effect (12). In our case hypokalemia and hypertension were not detected. Ambulatory blood pressure monitoring and echocardiography were normal. At the time of diagnosis, 10–15% of individuals with 17OHD are normotensive and/or normokalemic. Dundar et al. detected hypertension in approximately 75% of patients at the time of diagnosis in their study (10). The heterogeneity of hypertension and hyperkalemia can be explained by the variance in target tissue sensitivity of various cortisol precursors, which show mineralocorticoid activity. The response in females to increased DOC is lower (13). In one study; hypertension was detected in one of the two patients with the same ethnicity and the same mutation of complete 17OHD, while the other was reported to be normotensive. However, in this case, the obese patient also had hypertension. (14). Thus, the role of gender, environmental variables, and ethnicity may explain variations in the presence and severity of hypertension in 17OHD patients. Since hydrocortisone helps to reduce 11-DOC and ACTH, we do not expect hypertension to develop after treatment is started. Nevertheless, blood pressure should be monitored. One of the importance of early recognition and management of 17OHD is to prevent or alleviate the long-term morbidity associated with HT.

Aldosterone was low in our case. In 17OHD, the immediate precursors of aldosterone are elevated, but aldosterone tends to be low. 11-DOC is assumed to inhibit renin and aldosterone synthase, resulting in sodium retention and volume expansion. However, treatment of 17OHD with glucocorticoids resulted in normal aldosterone levels (15).

In 17OHD, findings of adrenal failure are rare, due to excessive production of corticosterone, which has a weak glucocorticoid effect. Excessive corticosterone masks the symptoms of cortisol deficiency (5). In our case, there were no clinical signs and symptoms of adrenal insufficiency. However, hyperpigmentation became prominent during chemotherapy. Glucocorticoid (hydrocortisone 10 mg three times daily) was administered after the diagnosis of 17OHD was established. Although it is known that adrenal insufficiency does not develop in these patients, our patient was receiving chemotherapy and other symptoms of adrenal insufficiency could have been observed in severe infections due to neutropenia.

Genetic counseling, psychiatric evaluation, and follow-up were suggested for our patient. Our patient had a novel homozygous Q80* variant in *CYP17A1*. Since this variant is expected to cause a severely truncated P450c17 enzyme, we might expect a complete 17OHD in our case. Reports suggest gonadectomy in adolescence is appropriate in 46, XY girls with complete 17OHD due to the risk of malignant transformation of the abdominal testes (1). We planned gonadectomy after a psychiatric evaluation. In addition, sex hormone replacement therapy is recommended in adolescence for secondary sexual development, maintenance of female sexual characteristics, and stimulation of epiphyseal closure (10).

Conclusion

Due to the low prevalence and the diverse clinical, biochemical, and molecular presentations, the early diagnosis of 17OHD can be missed. In the presence of unexplained hyperpigmentation and hypergonadotrotropic hypogonadism, the hypothalamic pituitary adrenal functions should be evaluated for 17OHD.

Authorship Contribution

N.T; Surgical and medical practices, data collection, analysis
İ.K; Surgical and medical practices, concept, data collection, analysis
N.Y; Surgical and medical practices, data collection
Ç.T; Surgical and medical practices, data collection
Ş.D; Data collection, analysis
E.S; Surgical and medical practices, design, analysis, literature research, writing

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Table 1. The biochemical and hormonal findings of the patient

Laboratory evaluation	Results	Reference range
Sodium (mmol/L)	142	136-145
Potassium (mmol/L)	3.9	3,5-4,5
FSH (mIU/mL)	41.55	2.1-11.1
LH (mIU/mL)	32.86	<11.9
ACTH (ng/L)	199.5	7.2-63.3
Cortisol (ug/dL)	0.59	50-250
Estradiol (pg/mL)	<5.00	6-27
Total testosterone (ng/dL)	<2.5	0-75
11-DOC (ug/L)	0.7	0-0.3
AMH (ng/mL)	16	1.7-104.5
17-OHP (ug/L)	0.15	<1
DHEAS (ug/L)	20.64	160-960
Androstenedione (ug/L)	0.034	0.42-1
Progesterone (ng/ml)	6.61	<0.33
Corticosterone (ug/L)	181	0.18-19.7
Aldosterone (ng/L)	<1.1	2.5-35.7
Renin (ng/dL)	<3.7	3.7-43.2

FSH: follicular-stimulating hormone; LH: luteinizing hormone; ACTH: adrenocorticotropic hormone; DHEA-S: dehydroepiandrosterone sulfate; 17OHP: 17a-hydroxyprogesterone; 11-DOC:11-Deoxyicorticosterone; AMH: anti-müllerian hormone

Figure 1. Skin color before treatment

Figure 2. Skin color after treatment