CASE REPORT

JCRPE Journal of Clinical Research in Pediatric Endocrinology

DOI: 10.4274/jcrpe.galenos.2024.2024-3-13
J Clin Res Pediatr Endocrinol 2026;18(Suppl 1):1-5

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

Niran Tekkeli[1], İlknur Kurt[2], Nevin Yalman[3], Çetin Timur[3], Şenol Demir[4], Elif Sağsak[5]

[1]Yeditepe University Faculty of Medicine, Department of Pediatrics, İstanbul, Türkiye
[2]Marmara University Faculty of Medicine, Department of Pediatric Endocrinology, İstanbul, Türkiye
[3]Yeditepe University Faculty of Medicine, Department of Pediatric Hematology, İstanbul, Türkiye
[4]Marmara University Faculty of Medicine, Department of Medical Genetics, İstanbul, Türkiye
[5]Yeditepe University Faculty of Medicine, Department of Pediatric Endocrinology, İstanbul, Türkiye

Cite this article as: Tekelli N, Kurt İ, Yalman N, Timur Ç, Demir Ş, Sağsak E. A rare presentation of 17α-hydroxylase/17,20-lyase deficiency in a patient with non-Hodgkin's lymphoma: a case report. J Clin Res Pediatr Endocrinol. 2026;18(Suppl 1):1-5

What is already known on this topic?

In 17α-hydroxylase/17,20-lyase deficiency (17OHD), patients are usually diagnosed during the adolescent period due to delayed puberty or amenorrhea. However, findings of adrenal failure are rare because of excessive production of corticosterone.

What this study adds?

Although clinical signs and symptoms of cortisol deficiency are not seen in 17OHD, hyperpigmentation may be observed in stressful situations. Hypergonadotropic 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. 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 hypergonadotropic hypogonadism while receiving chemotherapy.

Keywords: 17α-hydroxylase deficiency, *CYP17A1* gene, hyperpigmentation, hypergonadotropic hypogonadism, disorders/differences in sex development

Corresponding Author: Elif Sağsak, MD, Yeditepe University Faculty of Medicine, Department of Pediatric Endocrinology, İstanbul, Türkiye
E-mail: elif.sagsak@yeditepe.edu.tr **ORCID:** orcid.org/0000-0001-7121-1575
Conflict of interest: None declared
Received: 26.03.2024 **Accepted:** 05.06.2024 **Epub:** 10.10.2024 **Publication Date:** 22.05.2026

J Clin Res Pediatr Endocrinol
2026;18(Suppl 1):1-5

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 occurs 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 17OHD (P450c17) is essential for the synthesis of cortisol and sex steroids. This enzyme has 17α-hydroxylase and 17,20-lyase activities. The first reaction provides the transformation of pregnenolone and progesterone to 17α-hydroxypregnenolone and 17α-hydroxyprogesterone respectively. The second transforms 17α-hydroxysteroids to dehydroepiandrosterone (DHEA) 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 a late pubertal age (5). Although these patients also have absolute cortisol deficiency, they do not show clinical signs of cortisol deficiency because of the effect of corticosterone on the glucocorticoid receptor (6). However, in times of severe stress, classical findings of adrenal insufficiency may also occur in 17OHD. Here, we report the case of a 10 years and 6-months-old patient who was diagnosed with 17OHD while receiving treatment for non-Hodgkin's lymphoma (NHL) without common findings of the condition.

Case Report

Ten-and-a-half-year-old girl with NHL was referred to pediatric endocrinology as the ovaries were not seen on abdominal ultrasonography performed because of abdominal pain. Eight months earlier, 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 four years old and was evaluated as allergic. However, when 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 who were first-cousins. Anthropometric measurements were calculated by using reference values for Turkish children (7). On physical examination, her weight was 43 kg [+0.98 standard deviation score (SDS)], height was 150 cm (+1.3 SDS) and body mass index was 19.11 kg/m^2 (+0.57 SDS). Her blood pressure was 110/60 mmHg (95th percentile: 121/78 mmHg), and she was prepubertal. The external genital structure was typically female. There was hyperpigmentation in skin folds (Figure 1), and her liver was 7 cm palpable in the subcostal region. Pelvic ultrasound and magnetic resonance imaging 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, corticosterone, 11-DOC, and progesterone were found to be high, while cortisol, DHEA sulfate (DHEA-S), estradiol, total testosterone and 17-OH progesterone concentrations were low (Table 1). Serum sodium and potassium levels were normal. Karyotype analysis was performed by G-banding following 72 hour culture of 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 GmbH, Hilden, Germany 19300 Germantown Rd, Germantown, MD 20874, USA) following the manufacturer's protocol. Quantification of DNA concentration and purity assessment was carried out by spectrophotometric methods. Given the proband's clinical features and biochemical and hormonal findings, the *CYP17A1* gene sequence analysis was performed with the preliminary

Figure 1. Skin color before treatment

diagnosis of 17OHD. All coding exons and exon-intron regions of the *CYP17A1* gene were sequenced using next-generation sequencing technology (Miseq, Illumina Inc., San Diego, CA, USA). To call variants, sequencing data were aligned with the human reference genome, hg19. Genetic analysis identified a homozygous non-sense variation [(NM_000102): c.238C>T; p.Gln80*] 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) (8). The segregation analysis revealed that the parents were both heterozygous for the same *CYP17A1* c.238C>T(p.Gln80*) variant. Hydrocortisone treatment was initiated (10 mg/m^2/day in three doses). The proband underwent 24-hours blood pressure monitoring and echocardiography which were normal. The patient was referred for psychiatric consultation. After hydrocortisone treatment, hyperpigmentation regressed during 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 17OHD, patients are usually diagnosed during adolescence because of delayed puberty or amenorrhea. The diagnosis of 17OHD before puberty is very rare unless there is a known family history (9). The main reason for presentation at 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 (9,10). Our case is important because she was diagnosed at an early age without hypertension, delayed puberty or ambiguous genitalia. An abdominal ultrasound examination performed because of abdominal pain during treatment for NHL could not visualize any ovaries. Subsequently, we diagnosed hypergonadotropic hypogonadism. Evaluation of adrenal function should be included in the etiological evaluation of hypergonadotropic hypogonadism in girls, after excluding Turner syndrome (11). The patient had no Turner syndrome stigmata. Chemotherapy may also cause hypergonadotropic hypogonadism but because of the very short duration of chemotherapy before diagnosis of hypergonadotropic hypogonadism, we did not consider chemotherapy in the etiology.

Table 1. The biochemical and hormonal findings of the patient at presentation

Laboratory evaluation	Result	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
DHEA-S (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: follicle-stimulating hormone, LH: luteinizing hormone, ACTH: adrenocorticotropic hormone, DHEA-S: dehydroepiandrosterone sulfate, 17OHP: 17α-hydroxyprogesterone, 11-DOC: 11-deoxyicorticosterone, AMH: anti-Müllerian hormone

Biochemical investigations demonstrated that there were decreased concentrations of estradiol, total testosterone, DHEA-S, 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 even though the karyotype was 46, XY. Based on the clinical, biochemical, and molecular features, the patient was diagnosed with 17OHD. In cases of 17OHD, steroid synthesis in both the adrenal glands and gonads is impaired (12). This leads to complete female external genitalia in both sexes when there is complete enzyme deficiency.

Since ACTH and melanocyte-stimulating hormone 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, and 11β-hydroxylase deficiency (8). The presented case had mild hyperpigmentation, evident from the age of four years old. This color change was misdiagnosed as an allergic reaction and she used allergy medications which were ineffective. Furthermore, the proband's parents reported increased pigmentation since the initiation of chemotherapy for NHL which suggested increased stress and a compensatory increase in ACTH. Significant hyperpigmentation in the folds and darkening of the skin color decreased markedly approximately two weeks after hydrocortisone treatment was started (Figure 2). In cases of unexpected hyperpigmentation of the skin, especially in the skin folds, adrenal function should be checked.

In addition, increased ACTH leads to a elevated 11-DOC production. High levels of 11-DOC induce sodium and fluid retention and loss of potassium and hydrogen, and consequently hypertension, because of the potent mineralocorticoid effect of 11-DOC (13). In the presented 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. (10) reported hypertension in approximately 75% of patients at the time of diagnosis. 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 (14). 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 patient with hypertension was also obese (15). Thus, the role of gender, environmental variables, body habitus and ethnicity may explain variations in the presence and severity of hypertension in 17OHD patients. Since hydrocortisone helps to reduce 11-DOC and ACTH levels, hypertension is not expected to develop after treatment is started. Nevertheless, blood pressure should be monitored. One of the benefits of early recognition and management of 17OHD is to prevent or alleviate the long-term morbidity associated with hypertension.

Aldosterone was low in the presented 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 (16).

Figure 2. Skin color after treatment

In 17OHD, findings of adrenal failure are rare, because of excessive production of corticosterone, which has a weak glucocorticoid effect. Thus, excessive corticosterone in 17OHD tends to mask the symptoms of cortisol deficiency, as in the presented case (5). 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 the presented patient. There was a novel, homozygous Q80* variant in *CYP17A1*. Since this variant is expected to cause a severely truncated P450c17 enzyme, we might expect complete 17OHD. 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, if accepted, 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 (11).

Conclusion

Early diagnosis of 17OHD may be challenging because of the low prevalence of the condition and the diverse clinical, biochemical, and molecular presentations. In the presence of unexplained hyperpigmentation and hypergonadotropic hypogonadism, the hypothalamic-pituitary-adrenal axis should be evaluated to investigate 17OHD.

Ethics

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

Footnotes

Authorship Contributions

Surgical and Medical Practices: Niran Tekkeli, İlknur Kurt, Nevin Yalman, Çetin Timur, Elif Sağsak, Concept: İlknur Kurt, Design: Elif Sağsak, Data Collection or Processing: Niran Tekkeli, İlknur Kurt, Nevin Yalman, Çetin Timur, Şenol Demir, Analysis or Interpretation: Niran Tekkeli, Şenol Demir, Elif Sağsak, Literature Search: Niran Tekkeli, Elif Sağsak, Writing: Elif Sağsak.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Miller WL, Auchus RJ. The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. Endocr Rev. 2011;32:81-151. Epub 2010 Nov 4
2. Lieberman S, Warne PA. 17-hydroxylase: an evaluation of the present view of its catalytic role in steroidogenesis. J Steroid Biochem Mol Biol. 2001;78:299-312.
3. Auchus RJ. The genetics, pathophysiology, and management of human deficiencies of P450c17. Endocrinol Metab Clin North Am. 2001;30:101-119, vii.
4. Auchus RJ. Steroid 17-hydroxylase and 17,20-lyase deficiencies, genetic and pharmacologic. J Steroid Biochem Mol Biol. 2017;165:71-78. Epub 2016 Feb 6
5. Keskin M, Uğurlu AK, Savaş-Erdeve Ş, Sağsak E, Akyüz SG, Çetinkaya S, Aycan Z. 17α-hydroylase/17,20-lyase deficiency related to P.Y27*(c.81C>A) mutation in CYP17A1 gene. J Pediatr Endocrinol Metab. 2015;28:919-921.
6. Sun M, Mueller JW, Gilligan LC, Taylor AE, Shaheen F, Noczyńska A, T'Sjoen G, Denvir L, Shenoy S, Fulton P, Cheetham TD, Gleeson H, Rahman M, Krone NP, Taylor NF, Shackleton CHL, Arlt W, Idkowiak J. The broad phenotypic spectrum of 17α-hydroxylase/17,20-lyase (CYP17A1) deficiency: a case series. Eur J Endocrinol. 2021;185:729-741.
7. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, Baş F. Reference values for weight, height, head circumference, and body mass index in Turkish children. J Clin Res Pediatr Endocrinol. 2015;7:280-293.
8. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-424. Epub 2015 Mar 5
9. Kurnaz E, Kartal Baykan E, Türkyılmaz A, Yaralı O, Yavaş Abalı Z, Turan S, Bereket A, Çayır A, Guran T. Genotypic sex and severity of the disease determine the time of clinical presentation in steroid 17α-hydroxylase/17,20-lyase deficiency. Horm Res Paediatr. 2020;93:558-566. Epub 2021 Mar 29
10. Fontenele R, Costa-Santos M, Kater CE. 17α-hydroxylase deficiency is an underdiagnosed disease: high frequency of misdiagnoses in a large cohort of brazilian patients. Endocr Pract. 2018;24:170-178. Epub 2017 Nov 16
11. Dundar I, Akinci A, Camtosun E, Ciftci N, Kayas L. Presentation, diagnosis, and follow-up characteristics of 17α-hydroxylase deficiency cases with exon 1-6 deletion (founder mutation) in the CYP17A1gene: 20-year single-center experience. Sex Dev. 2023;17:43-50. Epub 2023 Jan 18
12. Voutilainen R, Miller WL. Developmental expression of genes for the stereoidogenic enzymes P450scc (20,22-desmolase), P450c17 (17 alpha-hydroxylase/17,20-lyase), and P450c21 (21-hydroxylase) in the human fetus. J Clin Endocrinol Metab. 1986;63:1145-1150.
13. Mula-Abed WA, Pambinezhuth FB, Al-Kindi MK, Al-Busaidi NB, Al-Muslahi HN, Al-Lamki MA. Congenital adrenal hyperplasia due to 17-alpha-hydoxylase/17,20-lyase deficiency presenting with hypertension and pseudohermaphroditism: first case report from Oman. Oman Med J. 2014;29:55-59.
14. Kawanishi H, Hasegawa Y, Nakano D, Ohkita M, Takaoka M, Ohno Y, Matsumura Y. Involvement of the endothelin ET(B) receptor in gender differences in deoxycorticosterone acetate-salt-induced hypertension. Clin Exp Pharmacol Physiol. 2007;34:280-285.
15. Keskin M, Uğurlu AK, Savaş-Erdeve Ş, Sağsak E, Akyüz SG, Çetinkaya S, Aycan Z. 17α-hydroylase/17,20-lyase deficiency related to P.Y27*(c.81C>A) mutation in CYP17A1 gene. J Pediatr Endocrinol Metab. 2015;28:919-921.
16. Bassett MH, White PC, Rainey WE. The regulation of aldosterone synthase expression. Mol Cell Endocrinol. 2004;217:67-74.