An easily missed diagnosis: 17-alpha-hydroxylase/17,20-lyase deficiency

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The *CYP17A1* gene encodes the enzyme P450c17, which mediates both 17α-hydroxylase and 17,20-lyase activities and is essential for production of cortisol and sex steroids. Loss-of-function mutations of this gene cause 17α-hydroxylase/17,20-lyase deficiency, characterized by hypertension, hypokalemia and sexual infantilism.

A 6-year-old phenotypically female patient presented with hypertension and hyperpigmentation. Her blood test results showed low cortisol and high adrenocorticotropic hormone (ACTH), progesterone, deoxycorticosterone and gonadotropin levels and were consistent with the diagnosis of 17α-hydroxylase/17,20-lyase deficiency. Her karyotype was 46XY. Genetic studies of the patient revealed a novel homozygous point mutation, c.1307G>A, within the coding sequence of the *CYP17A1* gene.

17α-hydroxylase/17,20-lyase deficiency should be considered in the differential diagnosis of hypertension in children and adolescents, and physical examination of these patients should be done very carefully.

Key words: 17α-hydroxylase/17,20-lyase deficiency,* CYP17A1 *gene, disorders of sex development.

17α-hydroxylase/17,20-lyase deficiency is a rare disease, accounting for about 1% of congenital adrenal hyperplasia (CAH) cases, characterized by hypertension and sexual infantilism and caused by loss-of-function mutations in the *CYP17A1* gene which is located on chromosome 10q24-q25. The *CYP17A1* gene encodes the enzyme P450c17, which mediates both 17α-hydroxylase and 17,20-lyase activities[1-3]. 17α-hydroxylase is required for the synthesis of cortisol; it catalyzes the 17α-hydroxylation reaction of pregnenolone and progesterone to 17α-hydroxypregnenolone and 17α-hydroxyprogesterone (17-OH progesterone), respectively. 17,20-lyase is essential for the production of sex steroids; it converts 17α-hydroxypregnenolone and 17-OH progesterone to dehydroepiandrosterone (DHEA) and androstenedione, respectively[1,4,5]. The steroid precursor products proximal to the enzymatic block are converted to progesterone and then to deoxycorticosterone (DOC) and corticosterone. DOC-mediated mineralocorticoid excess results in hypertension and hypokalemia and suppressed plasma renin activity and aldosterone levels[1-5]. Elevated corticosterone protects patients from cortisol insufficiency due to its activity at glucocorticoid receptors[1,2,4]. Patients with complete 17α-hydroxylase/17,20-lyase deficiency have external female genitalia regardless of whether the karyotype is 46,XY or 46,XX. The diagnosis may be missed in childhood, because 17α-hydroxylase/17,20-lyase deficiency is a very rare disorder and the classic features of CAH are not present; ambiguous genitalia occur only in partial insufficiency in

Table I. Standard Adrenocorticotropic Hormone Stimulation Test Results of the Patient

	Basal hormone values	Peak values after stimulation	Normal reference (for basal values)
ACTH (pg/ml)	176	-	0-46
Cortisol (μg/dl)	1.8	3.0	5-25
Progesterone (ng/ml)	7.5	12	0.1-0.35
17-OH progesterone (ng/ml)	0.64	0.73	0.03-0.9
Androstenedione (ng/ml)	>0.3	>0.3	0.08-0.5
DOC (ng/dl)	313.8	440.5	7.0-49.0
DHEA-S (μg/dl)	3.35	-	9-72

ACTH: Adrenocorticotrophic hormone, DHEA-S: Dehydroepiandrosterone sulfate, DOC: Deoxycorticosterone

46,XY individuals. If blood pressure (BP) is not assessed during physical examination, delayed puberty may be the first sign of this disease. If untreated, 17α-hydroxylase/17,20-lyase deficiency may lead to serious complications [1-5].

In this article we report a patient with 17α-hydroxylase/17,20-lyase deficiency who presented with hypertension. Molecular analysis of the *CYP17A1* gene revealed a novel c.1307G>A point mutation.

Case Report

A 6-year-old girl presented to our outpatient clinic with headache and fatigue. She was born at term after a normal pregnancy to consanguineous parents with no known family history of disorders of sex development (DSD). She had mild mitral valve insufficiency revealed by echocardiography that was done when she was one year old because of perioral cyanosis. Annual cardiology follow-up was recommended. One year before her presentation to our hospital, hypertension was detected on her routine cardiologic examination and antihypertensive therapy was started. The family showed poor adherence to therapy and did not complete the recommended investigations for the definitive diagnosis. On physical examination in our outpatient clinic, her BP was measured as 160/100 mmHg, and she was admitted to the hospital for further investigation and therapy. Her height was 126.1 cm (1.9 SDS), and her weight, 23.4 kg (1.4 SDS). She had low-set ears, a small chin, long philtrum and dark skin color. Cardiac auscultation revealed normal first and second heart sounds and a 2/6 systolic murmur over the apical area. The external genitalia were recorded as normal pre-pubertal female. There were no other abnormal findings on her physical examination.

Investigations including complete blood count, erythrocyte sedimentation rate, serum electrolytes, kidney function tests, thyroid hormone levels, urine test, urine catecholamine levels, electrocardiography, telegraphy, abdominal ultrasonography and renal Doppler ultrasonography were all normal. Echocardiography revealed mild mitral valve insufficiency with increased blood flow in the pulmonary artery branches and aorta, and mild increase in left ventricular septum thickness. Grade 1 hypertensive retinopathy was detected on ophthalmologic examination. Her 24-hour ambulatory BP monitoring showed a mean BP>99th percentile for her age and height. Her serum aldosterone level was high (836 pg/ml, normal: 10-160) and plasma renin activity low (0.32 ng/ml/hour, normal: 0.5-1.9). Antihypertensive treatment was started due to ongoing hypertension throughout the day and night and evidence of end organ damage.

Because of suppressed plasma rennin activity and high aldosterone levels, an endocrine disorder was suspected as the cause of her hypertension. Pediatric endocrinology consultation revealed that in addition to her dark skin color, there was prominent hyperpigmentation in her nipples, flexor areas and oral mucosa; additional tests were done. Her morning cortisol level was low and adrenocorticotrophic hormone (ACTH) level high; in addition, cortisol response was insufficient on the standard ACTH stimulation test (Table I). Her basal progesterone and DOC levels were very high and DHEA-S and androstenedione levels low (Table I). Her basal 17-OH progesterone level was

normal, but the response to ACTH stimulation was negligible (Table I). Her gonadotropin levels were high (LH, 3.1 mIU/ml; FSH, 43.5 mIU/ml). Pelvic ultrasonography and pelvic magnetic resonance imaging showed that she did not have a uterus or Fallopian tubes; a lesion of 10x5 mm, compatible with a gonad, was seen on the right inguinal region. Her karyotype was 46,XY. Human chorionic gonadotropin (hCG) testing showed low testosterone, DHEA-S and androstenedione response, and high progesterone response to stimulation (Table II). The patient was diagnosed with 17α-hydroxylase/17,20-lyase deficiency; hydrocortisone treatment was initiated in addition to the antihypertensive therapy. Her hypertension required continuation of medication during her 6-year follow-up in the pediatric endocrinology and nephrology outpatient clinics in spite of her normal steroid precursor values under the steroid treatment. No other cause for hypertension could be found.

The patient's gender identity was assessed by a child and adolescent psychiatrist, and with the agreement of the pediatric endocrinology, child and adolescent psychiatry, pediatric surgery, radiology and genetic units, it was decided to leave the gender identity as female, and an orchidectomy was done. The extracted gonad's pathology was compatible with immature testis tissue.

All 8 *CYP17A1* exons of the patient's probands as well as those of her parents were PCR-amplified and directly sequenced (Universitätsklinikum Schleswig-Holstein, Campus Kiel, Germany). Genetic studies revealed a novel homozygous point mutation, c.1307G>A, within the coding sequence of the *CYP17A1* gene. This mutation leads to a substitution of glycine (an amphoteric amino acid) for arginine (a basic charged polar amino acid) at position 46. Both parents were heterozygous for this mutation. This result was consistent with the diagnosis of 17α-hydroxylase/17,20-lyase deficiency.

Discussion

Disorders of sex development are defined as congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical[6]. The most common causes of DSDs are CAH, androgen insensitivity syndrome and mixed gonadal dysgenesis[7-11]. 17α-hydroxylase/17,20-lyase deficiency is a rare form of CAH; its true incidence is unknown, but may be around 1/50,000 to 1/100,000 in newborns[1]. Due to the rarity of this disorder, many doctors are not familiar with the symptoms, and there are many cases in the literature that were diagnosed at very late ages in spite of their characteristic symptoms[2,3,5,12]. Our patient was relatively fortunate in being diagnosed at the age of six, but her diagnosis had nonetheless been missed, since her hypertension had been detected one year previously; we may assume that the hypertension had started even earlier. Had her hyperpigmentation been noticed, the diagnosis of 17α-hydroxylase/17,20-lyase deficiency might have made before she was 6 years old.

Our patients' potassium levels were in low but within normal limits. Although her plasma renin activity was suppressed, her aldosterone concentration was high, making an accurate diagnosis using biochemical data difficult. Clinical and biochemical presentations of 17α-hydroxylase/17,20-lyase deficiency are highly variable; 10%–15% of patients are normotensive at diagnosis, and serum potassium

Table II. Human Chorionic Gonadotropin Test Results of the Patient

	Basal hormone values	Values after hCG stimulation	Normal reference (for basal values)
Testosterone (ng/ml)	0.04	0.06	<0.025-0.10
DHEA-S (μg/dl)	0.1	0.1	9-72
17-OH progesterone (ng/ml)	0.60	0.92	0.03-0.9
Progesterone (ng/ml)	0.6	7.3	0.1-0.35
Androstenedione (ng/ml)	<0.3	<0.3	0.08-0.5
Estradiol (pg/ml)	5	11.3	<15

DHEA-S: Dehydroepiandrosterone sulfate, hCG: Human chorionic gonadotropin

and aldosterone levels can be diverse[1,3,12]. High aldosterone levels in 17α-hydroxylase/17,20-lyase deficiency are considered to be due to cross-reactions between aldosterone and other mineralocorticoid precursors that are massively elevated in this disorder[3,12]. Some authors also suggest that increased ACTH may lead to high aldosterone levels in these patients[3].

More than 95 mutations in the *CYP17A1* gene have been identified in the Human Gene Mutation Database, including insertions, deletions, missense and nonsense mutations and splice site variants[3]. The phenotypic severity of this disease, including hypertension, hypokalemia and genital undervirilization in 46,XY subjects, varies depending on whether the activities of these enzymes are completely or partially lost, according to the type and localization of the mutation. Most mutations cause loss of function of both enzymes and impair gonadal and adrenal steroidogenesis together[3,13]. Our patient's clinical findings were compatible with loss of function of both 17α-hydroxylase and 17,20-lyase activities; genetic studies revealed a novel homozygous point mutation, c.1307G>A, within the coding sequence of the *CYP17A1* gene.

Treatment of the hypertension due to 17α-hydroxylase/17,20-lyase deficiency is glucocorticoid replacement delivered at a supraphysiological dose to suppress the mineralocorticoid precursor excess[1,4]. In the case of our patient, antihypertensive medication could not be discontinued at 6-year follow-up, despite her normal steroid precursor values under the steroid treatment. Short-term steroid replacement generally normalizes mineralocorticoid precursors, potassium levels and BP in 17α-hydroxylase/17,20-lyase deficiency[2,3,12]. Sometimes, however, a longer period of glucocorticoid use is needed to normalize BP. If hypertension is diagnosed late, secondary renovascular pathologies can develop and may cause persistent hypertension[1]. Our patient was only 6 years old at the time of diagnosis, so it is not clear whether this was the reason for her persistent hypertension, but no other cause could be identified.

Psychosocial problems are common in DSD patients because of the gender identity issues involved. Psychosexual development is influenced by multiple factors such as sex chromosome genes; timing, dose and type of androgen exposure; sex of rearing; social circumstances; and family dynamics[14]. Karyotype, gonadal function, phenotype, internal genitalia, potential for fertility and sexuality, risk of future malignancy and prenatal brain virilization are some of the many factors that should be taken into account when assessing gender in a child with DSD[14]. Each patient should be evaluated individually using a multidisciplinary approach, as in our case. Our patient was raised as female, and due to an enzymatic defect in a steroid pathway, she had no prenatal or postnatal brain virilization. After detailed psychiatric evaluation of the patient and the family, it was decided to leave the gender identity as female, and an orchidectomy operation was performed.

In conclusion, 17α-hydroxylase/17,20-lyase deficiency should be considered in the differential diagnosis of hypertension in children and adolescents, and physical examination should be done very carefully. Since the identification and early diagnosis of these patients is important for adequate management, BP measurement and assessment of pubertal status should be intrinsic parts of routine physical examination.

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