Discussion: Evaluation of our cohort with 17OHD revealed that, the diagnosis of 17OHD is mostly established at pubertal ages (14 years) unless the affected patients have severe hypertension or ambiguous genitalia. Although more than half of our patients were hypertensive at presentation, most common complaints of clinical presentation were absent puberty and amenorrhea. Nonetheless, the severe symptomatic hypertension and ambiguous genitalia due to partial 17OHD in 46,XY emerged as the factors for early clinical presentation of the condition.

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Genotypic Sex and Severity of the Disease Determine the Time of Clinical Presentation in Steroid 17α-hydroxylase/17,20-lyase Deficiency

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INTRODUCTION

Congenital adrenal hyperplasia (CAH) due to steroid 17α-hydroxylase deficiency (17OHD) (MIM # 202110) is a rare autosomal recessive disorder. The enzyme, cytochrome P450c17 catalyzes the 17α-hydroxylase and 17,20-lyase activities, which are involved in the biosynthesis of cortisol in the adrenal zona fasciculata and the generation of androgenic steroids and estrogens in the adrenal zona reticularis and in gonads. Various severities of molecular defects in the *CYP17A1* gene, which encodes P450c17 enzyme, are associated with the complete or partial 17OHD.

The metabolic signature of 17OHD includes low concentrations of cortisol, 11-deoxycortisol, dehydroepiandrosterone sulphate (DHEAS) and 17-hydroxyprogesterone together with elevated adrenocorticotropic hormone (ACTH), corticosterone, 11-deoxycorticosterone (DOC) and progesterone. The absence of secondary sexual characteristics or amenorrhea are the most common presenting symptoms of 17OHD due to deficiency of adrenal and gonadal sex steroids. The clinical manifestations of cortisol deficiency are not apparent due to the glucocorticoid effect of high corticosterone concentrations. Therefore, most of the previously reported cases have come to clinical attention at late pubertal ages.

AIM

Herein, we have evaluated the comprehensive clinical, hormonal and molecular characteristics of 12 patients with 17OHD to search the conditions related to early and late clinical presentation. Diagnostic challenges, follow-up characteristics, and treatment outcomes were discussed.

METHOD

Clinical data, steroid profiles by liquid chromatography-tandem mass spectrometry and Sanger sequencing of *CYP17A1* gene was evaluated in 12 patients with 17OHD diagnosed between 2004-2020.

RESULTS

Median age of diagnosis was 13.9 (range:0.04-29.5) years. All patients had consanguineous parents. Ten of 12 patients had 46,XY karyotype. The age range of the patients at the time of diagnosis was between 15 days and 25.9 years (median;13.95 years). Except one boy with partial 17OHD, all patients had female external genitalia hence raised as females. The clinical presentation of 17OHD was earlier (median age:7 years) in patients, who presented with severe hypertension, atypical genitalia or positive family history (n=6, 50%) than those without (median age:15.3 years; p=0.0005). The latter group presented with amenorrhea (n=6, 50%). Serum gonadotropin concentrations were elevated in patients >12 years (n=7), normal in pre-adolescents (n=4) and low in a patient who had a digenic inheritance of homozygous *CYP17A1* and *KISS1R* mutations. The clinical characteristics and biochemical results of the patients at the time of diagnosis are presented in Table 1 and Table 2. Clinical data of patients with 17OHD at the last evaluation is presented in Table 3.

Table 1. Clinical characteristics at the presentation and molecular results of patients with 17OHD.

F	P	Age (yrs)	External genitalia	Tanner stage	SBP/DBP (mmHg)	Presenting symptom	Other features	FSH (IU/L)	LH (IU/L)	Karyotype	*CYP17A1* mutation
F1	P1	2.4	Female	B1P1	135/85	HT	Bicuspid aortic valve	3.2	0.02	46,XY	**c.104_108delCCCTG (p.P35Rfs*15), homozygous**
F2	P2	14.3	Female	B1P1	140/95	Amenorrhea	-	70	38.2	46,XY	**c.238C>T (p.Q80*), homozygous**
	P3	6.8	Female	B1P1	140/100	Screening of siblings	-	11.4	0.3	46,XY	**c.238C>T (p.Q80*), homozygous**
F3	P4	13.6	Female	B2P1	115/75	Palpitation	Bicuspid aortic valve, short stature	11.4	13.7	46,XY	c.1283C>T (p.P428L), homozygous
	P5	7.3	Female	B1P1	105/75	Screening of siblings	History of hypokalemic metabolic alkalosis at 2.5 years of age	2.7	0.02	46,XX	c.1283C>T (p.P428L), homozygous
F4	P6	12.3	Female	B1P1	140/95	HT	Conversion disorder, asthma	84.7	22.3	46,XY	Exon 1-6 deletion, homozygous
F5	P7	25.9	Female	B1P1	110/75	Amenorrhea	Hypogonadotropic hypogonadism	1.3	0.15	46,XY	**c. 104-108delCCCTG (p.P35Rfs*15) in *CYP17A1* homozygous + c.969C>A (p.Tyr323*) in *KISS1R* homozygous**
F6	P8	0.04	Incompletely masculinized male	G1P1	NA	Incompletely masculinized genitals	-	0.23	0.54	46,XY	c.1487G>A (p.R496H), homozygous
F7	P9	15	Female	B4P1	150/100	Amenorrhea	-	35.4	24.8	46,XY	**Exon 1-5 deletion, homozygous**
F8	P10	15	Female	B3/2P1	120/70	Small breasts, menstrual irregularity	-	15.2	18.2	46,XX	c.716G>A (p.R239Q), homozygous
F9	P11	16.5	Female	B1P1	150/100	Amenorrhea	-	47.7	35.2	46,XY	Exon 1-6 deletion, homozygous
F10	P12	15.7	Female	B1P1	180/160	Amenorrhea	Headache	85.9	45.1	46,XY	NA

Abbreviations: F= Family, P= Patient,Yrs=Years, BMD= bone mineral density, TH= Target height, SDS= standard deviation score, B: Breast development scale according to Tanner stage, G: Genital development scale according to Tanner stage, P: Pubarcheal development scale according to Tanner stage, HT: Hypertension, NA: not available, SBP= Systolic blood pressure, DBP= Diastolic blood pressure. Novel mutations are shown with bold characters. Normal range for FSH; Males: 1.7-12, Females:1.5-12 IU/L and for LH; Males: <0.2-7, Females:0.2-8 IU/L. Novel variants are marked in bold.

Table 2. Adrenocortical steroid hormone measurements by LC-MS/MS in the patients with 17OHD compared to the control group

		Patients with 17OHD (n=11)			Healthy control (n= 210)			*p* value
		Median	IQR		Median	IQR		
Pathways of adrenal steroid synthesis	Hormones		25%	75%		25%	75%	
Minerolocorticoid Pathway	Pregnenolone (ng/mL)	0.374	0.029	1.536	0.046	0.012	0.161	<0.0001
	Progesterone (ng/mL)	1.776	0.636	2.243	0.058	0.029	0.109	0.001
	11-Deoxycorticosterone (ng/mL)	1.401	0.668	2.265	0.035	0.018	0.061	<0.0001
	Corticosterone (ng/mL)	98.01	81.85	118	5.031	3.224	7.345	<0.0001
	Aldosterone (ng/mL)	0.063	0.020	0.221	0.016	0.006	0.040	0.003
Glucocorticoid Pathway	17OH-Pregnenolone (ng/mL)	0.225	0.145	0.759	0.215	0.056	0.846	0.57
	17OH-Progesterone (ng/mL)	0.013	0.005	0.183	0.295	0.137	0.471	0.08
	11-Deoxycortisol (ng/mL)	0.651	0.075	10.42	0.254	0.133	0.440	<0.0001
	Cortisol (ng/mL)	0.232	0.124	14.28	103.9	72.37	155.4	<0.0001
	Cortisone (ng/mL)	0.035	0.0125	1.162	24.25	18.01	29.59	<0.0001
Androgen Pathway	DHEA (ng/mL)	0.305	0.139	0.473	1.046	0.227	2.445	0.004
	DHEAS (ng/mL)	23.85	10.18	40.13	431.7	173	1112	0.0009
	Androstenedione (ng/mL)	0.016	0.003	0.019	0.25	0.108	0.715	0.002
	Androsterone (ng/mL)	0.195	0.040	0.782	0.119	0.031	0.474	0.68

IQR: Interquartile range, DHEA: Dehydroepiandrosterone, DHEAS: Dehydroepiandrosterone sulfate.

Table 3. Clinical data of patients with 17OHD at the last evaluation

F	P	Age (yrs)	Follow-up (yrs)	Tanner stage	SBP/DBP (mmHg)	Treatment	Gonadectomy
F1	P1	3.76	1.36	B1P1	130/80	HC, Amlodipin	Yes
F2	P2	15.6	1.3	B2P1	135/95	HC, Amlodipin, Estradiol	In progress
	P3	7.5	0.76	B1P1	140/90	HC, Amlodipin	In progress
F3	P4	14.75	1.15	B3P2	110/70	HC, Estradiol	In progress
	P5	8.34	1.04	B1P1	100/70	HC	In progress
F4	P6	14.41	2.11	B3P3	135/95	HC, Amlodipin, Estradiol	The gonads are not visualized by laparotomy, and laparoscopy.
F5	P7	28	2.1	B4P4	110/70	HC, E2+Prog, Calcium, Vitamin D	She rejected to undergo laparotomy, and laparoscopy.
F6	P8	6.5	6.46	G1P1	108/70	HC	No
F7	P9	20.8	5.8	B5P5	120/80	HC, E2+Prog, Calcium, Vitamin D	Yes
F8	P10	26	11	B5P5	107/80	HC, E2+Prog, Calcium, Vitamin D	No
F9	P11	16.7	0.2	B2/3P1	150/97	HC, Spironolactone, Estradiol, Calcium, Vitamin D	In progress
F10	P12	15.8	0.1, died due to hypertensive encephalopathy	B1P1	180/160	HC, Spironolactone, Amlodipine	No

Abbreviations: F= Family, P=Patient, Yrs=years, BMD= bone mineral density, TH= Target height, SDS= standard deviation score, B: Breast development scale according to Tanner stage, G: Genital development scale according to Tanner stage, P: Pubarcheal development scale according to Tanner stage, HC: Hydrocortisone, E2: Estradiol, Prog: Progesterone, NA: not available, SBP= Systolic blood pressure, DBP= Diastolic blood pressure.

DİSCUSSİON

Evaluation of our cohort with 17OHD revealed that, the diagnosis of 17OHD is mostly established at pubertal ages (14 years) unless the affected patients have severe hypertension or ambiguous genitalia. Although more than half of our patients were hypertensive at presentation, most common complaints of clinical presentation were absent puberty and amenorrhea. Nonetheless, the severe symptomatic hypertension and ambiguous genitalia due to partial 17OHD in 46,XY emerged as the factors for early clinical presentation of the condition. This relatively large series of 17OHD demonstrated that early diagnosis is associated with particular clinical manifestations including severe hypertension in both 46,XX and 46,XY and inadequate virilization of external genitalia in 46,XY patients Family screening provide early diagnosis and management of 17OHD in yet asymptomatic 46,XY and 46,XX cases. Surveillance of adrenal functions and 17OHD is warranted in all cases with absent puberty and/or amenorrhea especially in 46,XX cases. Finally, the reported cases herein contribute to molecular and phenotypic repertoire of 17OHD.