ADRENOCORTICAL HORMONE PROFILES DO NOT PREDICT THE MOLECULAR ETIOLOGY IN NON-CAH PRIMARY ADRENAL INSUFFICIENCY

T. SEVEN MENEVSE[1], Y. KENDIR DEMIRKOL[2], B. GURPINAR TOSUN[1], E. BAYRAMOGLU[3], M. YILDIZ[4], S. ACAR[5], S. ERISEN KARACA[6], Z. ORBAK[7], A. ONDER[8], E. SOBU[9], AHMET ANIK[10], Z. ATAY[11], F. BUGRUL[12], K. DEMIR[13], D. DOGAN[14], H. C. EMEKSIZ[8], H. KIRMIZIBEKMEZ[15], N. OZCAN MURAT[16], A. YAMAN[17], S. TURAN[1], A. BEREKET[1], T. GURAN[1]

[1]Marmara University, School of Medicine, Istanbul, Turkey, [2]Umraniye Research and Training Hospital, University of Health Sciences, Istanbul, Turkey, [3]Haseki Training and Research Hospital, Istanbul, Turkey, [4]Istanbul University, School of Medicine, Istanbul, Turkey, [5]Behcet Uz Education and Research Hospital, Izmir, Turkey, [6]Duzce University, School of Medicine, Bolu, Turkey, [7]Ataturk University, School of Medicine, Erzurum, Turkey, [8]Medeniyet University, School of Medicine, Istanbul, Turkey, [9]Kartal Training and Research Hospital, Istanbul, Turkey, [10]Aydin Adnan Menderes University, School of Medicine, Aydin, Turkey, [11]Istanbul Medipol University, School of Medicine, Istanbul, Turkey, [12]Selcuk University, School of Medicine, Konya, Turkey, [13]Dokuz Eylul University, School of Medicine, Izmir, Turkey, [14]Onsekiz Mart University, School of Medicine, Canakkale, Turkey, [15]Umraniye Research and Training Hospital, University of Health Sciences, Istanbul, Turkey, [17]Derince Research and Training Hospital, Kocaeli, Turkey, [17]Gungoren Hospital, Istanbul, Turkey

P1-2

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PATIENTS AND DESIGN

- Forty-one children (19 females, median age: 3 months, range: 0-8 years) with non-CAH PAI of unknown etiology from 16 tertiary pediatric endocrinology clinics.
- Patients with CAH, adrenoleukodystrophy, autoimmune adrenal insufficiency or obvious syndromic PAI on clinical and biochemical assessment were excluded.
- Genetic analysis was performed using either targeted gene panel or whole-exome sequencing.
- Plasma adrenal steroids were quantified by liquid chromatography-mass spectrometry and compared to that of controls.

RESULTS

- Molecular diagnosis was found in 11 genes in 29 (70.7%) cases.
- The range of genetic etiologies found in this cohort were: *StAR* (n=6; 20%), *MC2R* (n=6; 20%), *NNT* (n=3; 10%), *NR0B1/DAX1* (n=3; 10%), *CYP11A1* (n=2; 7%), *MRAP* (n=2; 7%), *SGPL1* (n=2; 7%), *ABCD1* (n=1; 3%), *AIRE* (n=1; 3%), *AAAS* (n=1; 3%), and *HSD3B2* (n=2; 7%).
- In 12 patients whose genetic etiology could not be found by TPS, further diagnosis was not be achieved by WES.

Table 1. Deficiency of adrenocortical steroids according to underlying molecular defect in patients with rare causes of PAI.

Gene (Chromosome locus)	Variant	n	Age of diagnosis	GC deficiency	MC deficiency	Sex steroid deficiency		Elevated TSH	IUGR / Short stature
						Gonadal	Adrenal		
MC2R (18p11.21)	c.455C>A (p.T152K) c.560del (p. V187fs) c. 476C>A (p.T159K)	2 2 2	6.25 years – 4 days 4 days – 3 months 2.48 years – 14 days	6/6	0/6	0/2 0/2 0*/2	2/2 2/2 2/2	1/2 1/2 2/2	0/1 0/0 0/0
STAR (8p11.23)	c.505G>A (p.E169K) c.470T>C (p.L157P)	3 3	3 days – 5 days – 5 months 1 month – 2 months – 2 months	6/6	6/6	3/3 3/3	3/3 3/3	1/3 0/3	1/0 0/0
NNT (5p12)	**exon 12-14 deletion** **c.259C>T (p.Q87*)** **c.2507G>A (p.G836D)**	1 1 1	1.5 years 6 months 1.48 years	3/3	0/1 1/1 0/1	0/1 0/1 0/1	1/1 1/1 1/1	0/1 0/1 0/1	0/0 1/0 0/0
NR0B1 (Xp21.2)	c.1075C>T (p.Q359*) c.1210C>T (p. Q404*) exon 1-2 deletion	1 1 1	1.5 years 2.5 years 1.5 years	3/3	3/3	1/1 1/1 1/1	1/1 1/1 1/1	0/1 0/1 0/1	0/0 1/0 0/0
CYP11A1 (15q24.1)	**c.461T>C (p.L154P)** c.1351C>T (p.R451W)	1 1	2 days 1.66 years	2/2	2/2	1/1 0/1	1/1 1/1	0/1 0/1	0/0 1/0
MRAP (21q22.11)	c.106 +1del **c.106 + 2dupT**	1 1	2 days 1.4 years	2/2	0/2	0/1 */1	1/1 1/1	0/1 1/1	0/0 0/0
SGPL1 (10q22.1)	c.1018C>T (p.R340W) **c.518T>A (p.L173Q)**	1 1	5 months 4 months	2/2	2/2	1/1 0/1	1/1 1/1	1/1 1/1	0/1** 0/1**
ABCD1 (Xq28)	**c.1772G>T (p.R591L)**	1	8 years	1	0	0/1	1/1	0/0	0/0
AIRE (21q22.3)	c.415C>T (p.R139*) / c.260T>C (p.L87P)	1	4.5 years	1	1	1/1	1/1	1/1	0/1
AAAS (12q13.13)	c.1333C>T (p.R478*)	1	4.5 years	1	0	*/1	1/1	0/1	0/0
HSD3B2 (1p12)	c.1003C>T (p.R335*) **c.939del (p.F314Sfs*54)** / c.745C>T (p.R249*)	1 1	1 month 1 month	2/2	2/2	0/1 0/1	0/1 0/1	0/1 1/1	0/0 1/0

RESULTS

Table 2. Adrenal steroid hormones of PAI patients with identified molecular etiologies compared to control group

	Patients (n=29)		Control (n=324)		
(ng/mL)	median	range	median	range	p
Aldosterone	0.06	0.007-0.70	0.198	0.002-0.982	0.0002
Cortisol	0.891	0.021-77.5	31.08	1.681-248.8	0.0003
DHEA-S	4.22	0.308-2757	132.1	5.609-978.1	0.5301
Corticosterone	0.057	0.002-5.12	0.926	0.025-19.62	0.0059
11-Deoxycortisol	0.029	0.001-2.03	0.231	0.028-2.094	0.0021
Androstenedione	0.013	0.001-0.42	0.073	0.001-0.824	0.2815
11-Deoxycorticosterone	0.017	0.001-0.55	0.035	0.002-3.085	0.4476
DHEA	0.112	0.01-35.9	0.626	0.012-28.07	0.5164
17OH-Pregnenolone	0.105	0.034-46.55	0.506	0.033-9.487	0.0043
17OH-Progesterone	0.013	0.002-1.934	0.214	0.001-2.728	0.0852
Progesterone	0.021	0.003-0.174	0.027	0.001-1.684	0.2966
Androsterone	0.44	0.004-10.01	0.97	0.004-24.56	0.9453
Pregnenolone	0.126	0.017-51.97	0.421	0.042-10.19	0.0024
Cortisone	0.426	0.026-23.09	29.3	1.376-165.9	<0.0001
21-Deoxycortisol	0.031	0.003-0.211	0.086	0.001-0.944	0.022

- Patients with solved molecular etiologies had lower concentrations of steroids than healthy infants, who has physiologically low steroids. The difference was most significant for aldosterone, cortisol, cortisone, corticosterone, pregnenolone, 17OH-pregnenolone, 11-deoxycortisol, 21-deoxycortisol**.**
- Plasma cortisol<4 ng/mL, cortisone<11 ng/mL, and corticosterone<0.11 ng/mL had >95% specificity to segregate non-CAH PAI patients compared to control groups (p<0.0001, area under the ROC curve: 0.96, 0.88, 0.87, respectively)

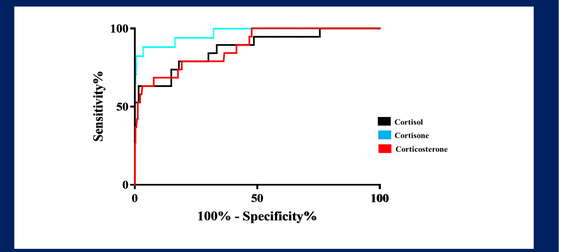

Figure 1. Specificity and sensitivity of cortisol, cortisone and corticosterone in the diagnosis of PAI

RESULTS

Table 3. Comparison of clinical and biochemical characteristics of PAI patients with solved or unsolved etiology.

	PAI solved (n=29)	PAI unsolved (n=12)	p
Age of diagnosis (yrs)	1.3 ± 0.3	5.7 ± 2.1	0.005**
Consanguinity of parents (n)	23	3	0.001**
MC deficiency (n)	17	7	0.98
Sex steroid deficiency (n)			
Gonadal	9	1	0.12
Adrenal	28	11	0.5
Karyotype (n)			
46,XX	10	2	0.25
46,XY	19	10	
Legal sex (n)			
Female	15	2	0.03*
Male	14	10	
ACTH (N=10-60 pg/mL)	1132 ± 55.14	992.7 ± 204.8	0.38
Cortisol (µg/dL)	0.8 ± 0.3	0.4 ± 0.1	0.002**
Cortisone (ng/mL)	3.8 ± 1.6	24.2 ± 5.1	0.0001***
Corticosterone (ng/mL)	0.20 ± 0.06	1.38 ± 0.40	<0.0001****
11-Deoxycorticosterone (ng/mL)	0.02 ± 0.007	0.10 ± 0.05	0.02*

CONLUSION

- Adrenocortical hormone profiles determined by LC-MS/MS which demonstrate significantly low glucocorticoids, mineralocorticoids and adrenal androgens, are highly sensitive for the recognition of non-CAH PAI even at early infancy, but the specificity to indicate a definitive molecular etiology is low.
- Targeted gene panel sequencing is a first-line approach in the molecular diagnosis of non-CAH PAI with high efficacy.
- Nevertheless, lower ACTH, absent parental consanguinity, late-onset of diagnosis and a less severe deficiency profile of steroid hormones decreases the probability of achieving the genetic diagnosis.

CONTACT INFORMATION

Professor Tulay Guran, MD
Marmara University School of Medicine,
Department of Pediatric Endocrinology and Diabetes
Fevzi Cakmak MhNo 41. 34899
Ustkaynarca/Pendik
Istanbul, Turkey

Tel: +90 2166254545
Fax: +90 2164168855
tulayguran@yahoo.com
tulay.guran@marmara.edu.tr