P2-189

The etiological spectrum of congenital adrenal hyperplasia based on molecular genetic analyses

Jin-Ho Choi[1], Ja Hye Kim[3], Eungu Kang[1], Ja Hyang Cho[1], Gu-Hwan Kim[2], Han-Wook Yoo[1]

[1]Department of Pediatrics, [2]Medical Genetics Clinic and Laboratory, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, [3]Department of Pediatrics, Hanyang University College of Medicine, Guri, Korea

Introduction

- Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders characterized by a defect in cortisol biosynthesis.
- The most common form of CAH is the 21-hydroxylase deficiency (21-OHD). However, the incidence and the etiologic spectrum of other forms of CAH were not reported in Korea.

Objectives

- To describes the etiological distribution of CAH
- To evaluate the clinical characteristics and age at first presentation of CAH in a single academic center

Methods

- This study included 189 patients with all forms of CAH.
- The diagnosis was confirmed by the clinical features, biochemical data, and molecular genetic analysis for the *CYP21A2*, *StAR*, *CYP17A1*, and *POR* genes.

Results

- Frequencies of each form of congenital adrenal hyperplasia.

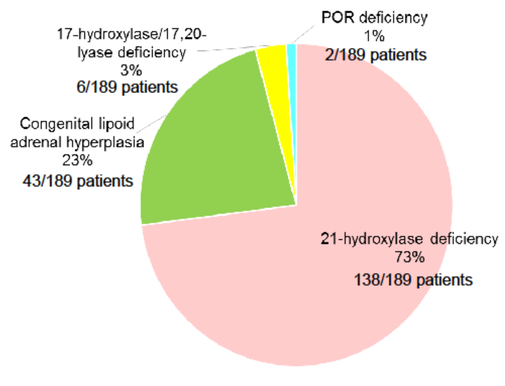


Fig. 1. Of a total of 189 patients, 138 patients (73%) from 128 families were 21-OHD (104 salt-losing, 33 simple-virilizing, and 1 non-classic forms), 43 (23%) from 41 unrelated families had *StAR* defect, six (3%) had 17-hydroxylase/17,20-lyase deficiency, and two (1%) had P450 oxidoreductase (POR) deficiency.

- Clinical characteristics and molecular analysis of CYP21A2 in 138 patients with 21-OHD.

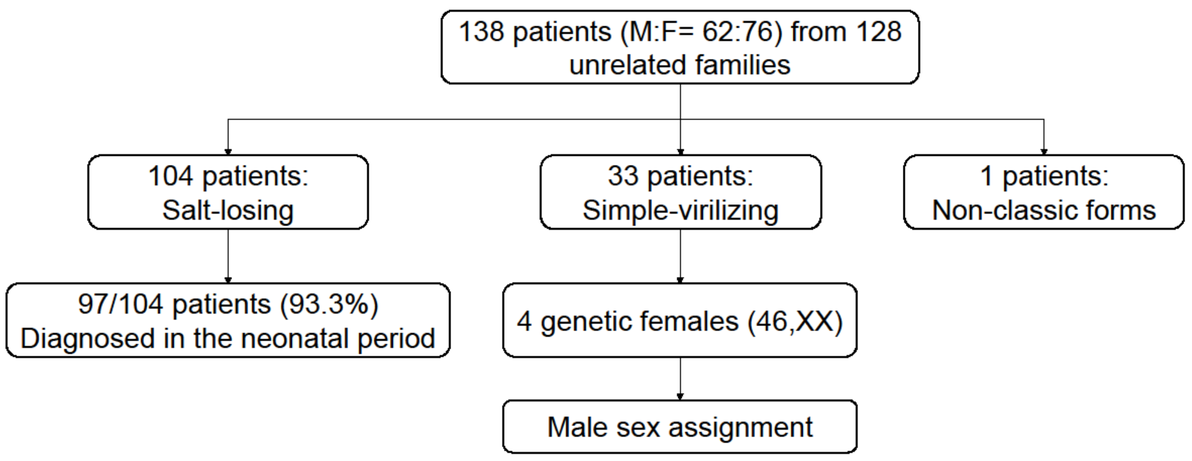


Fig. 2. Outcomes of patients with 21-OHD. 97 patients with salt-losing 21-OHD (97/104, 93.3%) were diagnosed in the neonatal period. Most girls of 21-OHD (75/76, 98.7%) presented with genital virilisation, whereas most boys (38/62, 61.3%) presented with salt-losing phenomenon within the first month of life. Four genetic female (46,XX) with simple virilizing form of 21-OHD were assigned as male because of delayed diagnosis.

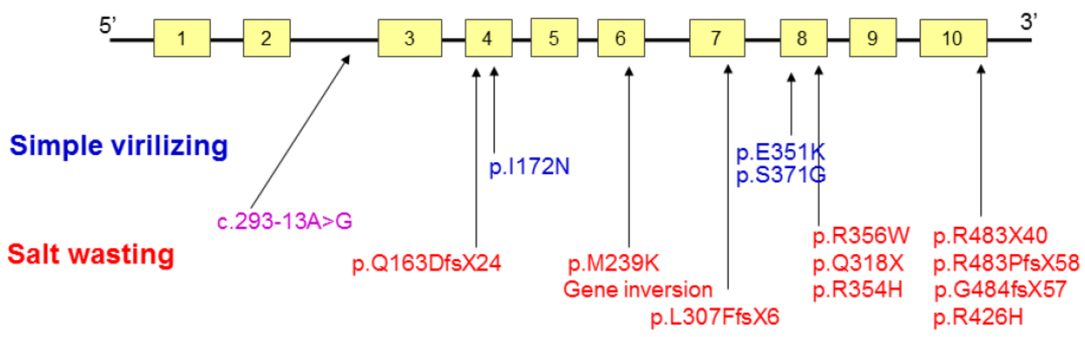


Fig. 3. Mutation spectrum of *CYP21A2* gene in patients with 21-OHD according to clinical phenotypes.

- 43 patients with congenital lipoid adrenal hyperplasia (CLAH) from 41 unrelated families
  - ➢ 8 different mutations in the *StAR* gene from 41 unrelated families
  - ➢ c.772C>T (p.Q258*): The most common *StAR* mutation in Korea (87.8%) by founder effect

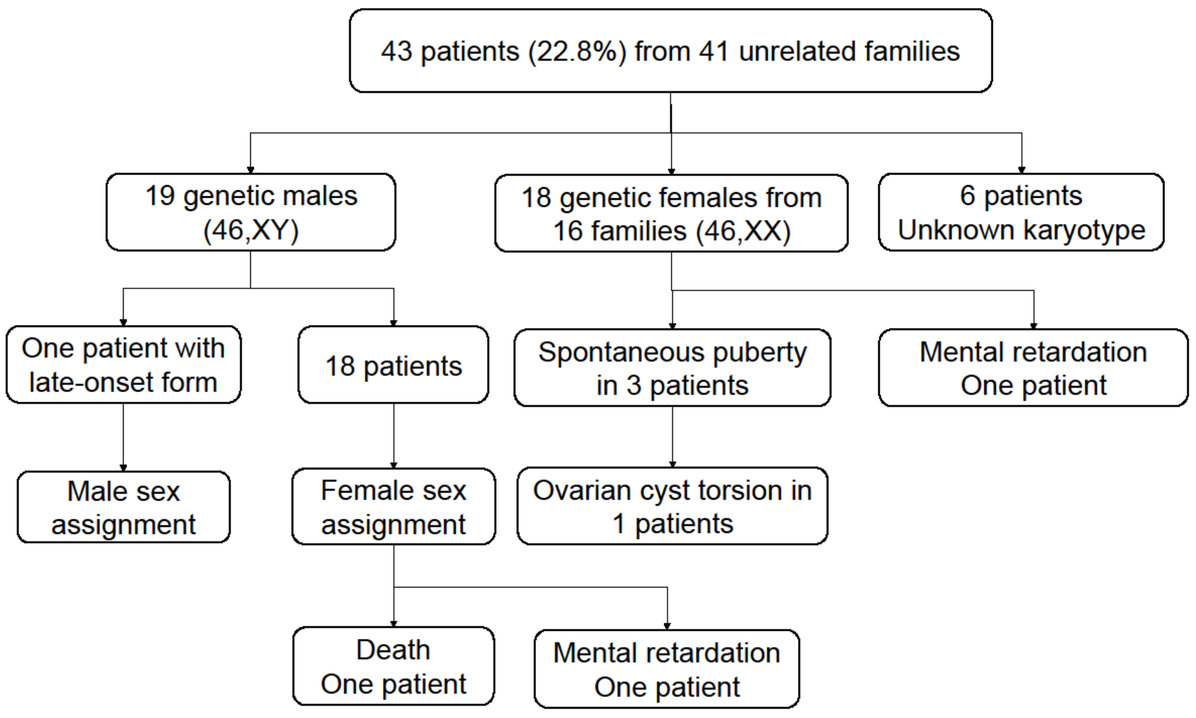


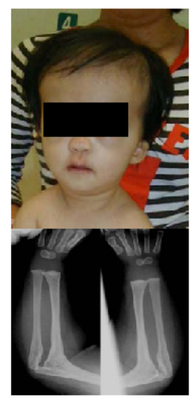
Fig. 4. Outcomes of patients with CLAH. Most patients (40/43, 93%) with StAR defect presented with adrenal crisis in the neonatal period, while 3 late-onset patients showed skin hyperpigmentation after age 2 years.

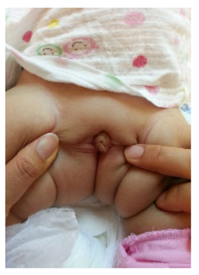
- Six patients with 17α-hydroxylase/17,20-lyase deficiency
  - ➢ Hypertension and primary amenorrhea during adolescent period

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age at diagnosis	14y 11mo	19y 2mo	15y	18y	42y	14y
Height SDS/weight SDS	-0.61/-0.16	-1.50/-2.57	3.08/1.37	0.85/2.60	1.85/1.95	2.00/1.88
BP, mmHg	180/100	171/115	170/100	140/90	208/150	150/90
Na/K, mEq/L	137/3.5	133/3.7	145/3.5	147/3.0	144/3.7	140/2.1
LH/FSH, mIU/mL	38.3/123	61.5/60.4	26.7/13.2	15.1/6.6	6.8/37.8	20/52
Estradiol, pg/mL	10.0	10.0	24	11	12	18
Testosterone, ng/mL	0.05	0.08	<0.1	<0.1	<0.1	ND
Progesterone, ng/mL (0.1-1.3)	10.7	2.4	6.7	7.0	16.5	9.9
ACTH, pg/mL (0-60)	162	510	211	189	344	34.6
Cortisol, μg/dL (5-25)	1.1	3.3	1.7	1.3	0.8	1.4
11-DOC ng/mL (0.03–0.33)	ND	ND	3.5	1.48	2.3	0.51
Renin, ng/mL/hr (0.68-1.36)	0.16	3.5	0.1	0.1	0.4	0.3
Aldosterone, pg/mL (70-300)	298	215	136	70	176	59.8
Karyotype	46,XY	46,XY	46,XX	46,XX	46,XY	46,XX
CYP17A1 mutation	p.H373L/ p.H373L	p.H373L/ p.W406L	p.H373L/ p.Y329fs	p.H373L/ p.Y329fs	p.H373L/ p.Y329fs	p.H373L /p.A174E

- Two girls with P450 oxidoreductase (POR) deficiency
  - ➢ Adrenal insufficiency, ambiguous genitalia, and craniosynostosis

	Case 1	Case 2
Age/Sex	7 months/Female	3 months/Female
Skeletal features	Craniosynostosis, Radiohumeral synostosis	None
Genitalia	Clitoromegaly	Partial fusion of labia majora
Maternal virilization	Denied	Not assessed
ACTH, pg/mL	290	415
Cortisol, μg/dL	9.3 → 9.6	13.4 → 26.2
17-OHP, ng/dL	2240 → 3630	28 → 83
DHEA-S, μg/dL (5-20)	9.9	43.0
Testosterone, ng/dL	0.8	0.1
Renin, ng/ml/hr (2.35-37)	1.4	6.1
Karyotype	46,XX	46,XX
POR gene	p.R457H/p.I444fs*449	p.R457H/p.R457H





Conclusions

- The most common cause of CAH was 21-OHD. Interestingly, lipoid CAH is the second common because of the founder mutation (p.Q258X) in Korea.
- Nationwide surveillance is needed to estimate the incidence and precise distribution of diverse etiology of CAH, though newborn screening for 21-OHD is introduced.

Disclosure statement

The authors have nothing to disclose.

ESPE 2015
189--P2
Adrenals and HPA Axis
Jin-Ho Choi
DOI: 10.3252/pso.eu.54espe.2015
Poster presented at: ESPE 2015 BARCELONA
PosterSessionOnline.com