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

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

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.

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
- 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
- Age at diagnosis: 14y 11mo
- Height SDS: -0.01
- BP: 117/75
- Renin, ng/mL: 0.95
- Aldosterone, pg/mL: 33.8
- Testosterone, ng/mL: 0.05
- Progesterone, ng/mL: 1.07
- ACTH, pg/mL: 162
- Cortisol, ug/dl: 1.1
- 11-DOC ng/mL: 0.33
- Renin, ng/mL: 0.16
- Aldosterone, pg/mL: 288
- Karyotype: 46,XY
- CYP17A1 mutation: p.H373L

Case 2
- Age at diagnosis: 14y 2mo
- Height SDS: -1.03
- BP: 117/75
- Renin, ng/mL: 1.07
- Aldosterone, pg/mL: 33.8
- Testosterone, ng/mL: 0.05
- Progesterone, ng/mL: 1.07
- ACTH, pg/mL: 162
- Cortisol, ug/dl: 1.1
- 11-DOC ng/mL: 0.33
- Renin, ng/mL: 0.16
- Aldosterone, pg/mL: 288
- Karyotype: 46,XY
- CYP17A1 mutation: p.H373L

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

Case 1
- Age/Sex: 7 months/Female
- Skeletal features: Craniosynostosis, Radiohumeral synostosis
- Genitalia: Clitoromegaly
- Maternal virilization: Partial fusion of labia majora
- ACTH, pg/mL: 290
- Cortisol, ug/dl: 9.3
- 17-OHP, ng/dl: 2240
- DHEA-S, ug/dl: 9.9
- Testosterone, ng/dl: 0.8
- Renin, ng/mL: 1.4
- Karyotype: 46,XX
- POR gene: p.R457H

Case 2
- Age/Sex: 3 months/Female
- Skeletal features: Craniosynostosis, Radiohumeral synostosis
- Genitalia: Partial fusion of labia majora
- Maternal virilization: Not assessed
- ACTH, pg/mL: 415
- Cortisol, ug/dl: 9.3
- 17-OHP, ng/dl: 262
- DHEA-S, ug/dl: 9.9
- Testosterone, ng/dl: 0.8
- Renin, ng/mL: 1.4
- Karyotype: 46,XX
- POR gene: p.R457H

Conclusions
- The most common cause of CAH was 21-OHD. Interestingly, lipid 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.