P2-710

Endocrine dysfunctions in children with CHARGE syndrome

Jin-Ho Choi[1], Eungu Kang[1], Yoon-Myung Kim[1], Gu-Hwan Kim[2], Han-Wook Yoo[1]

[1]Department of Pediatrics, [2]Medical Genetics Center, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Korea

Introduction

- CHARGE (Coloboma, Heart defects, choanal Atresia, Retardation of growth and development, Gonadal defects, and Ear/hearing abnormalities) syndrome (OMIM 214800) is a complex of congenital malformations affecting multiple organ systems caused by mutations in *CHD7* (chromodomain helicase DNA binding protein 7, OMIM 608892).
- Hypogonadism, growth failure with or without growth hormone (GH) deficiency, and hypothyroidism have been reported as endocrinological defects in patients with CHARGE syndrome.

Objectives

- This study was performed to evaluate endocrine dysfunctions including hypogonadotropic hypogonadism, short stature, or hypothyroidism in patients with CHARGE syndrome.

Methods

- Twenty three patients (15 males and 8 females) with CHARGE syndrome were included.
- A diagnosis of CHARGE syndrome was made according to the diagnostic criteria by Verloes.

Table 1. Verloes' diagnostic criteria for CHARGE syndrome

Major	Coloboma Choanal atresia Hypoplastic semicircular canals
Minor	Rhombencephalic dysfunction Abnormal external or middle ear Mental retardation Hypothalamic-pituitary dysfunction Malformation of mediastinal organs (heart and esophagus)
Diagnosis	**Typical CHARGE**: 3 major or 2 major and 2 minor **Partial/Incomplete CHARGE**: 2 major and 1 minor **Atypical CHARGE**: 2 major or 1 major and 3 minor

Verloes A. Am J Med Genet A 2005;133A(3):306–308

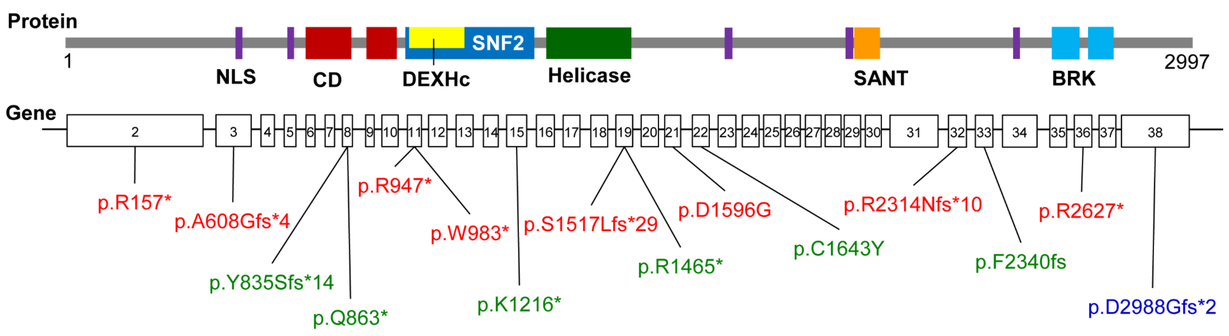
- All coding exons (2-38) and exon-intron boundaries of the *CHD7* were amplified by PCR and directly sequenced in 18 patients who agreed to underwent molecular analysis.
- Clinical features and endocrine functions were evaluated by retrospective chart review.

Results

- Eleven patients fulfilled the criteria for typical CHARGE syndrome, two patients for partial/incomplete, and the remaining 10 patients were atypical CHARGE syndrome by Verloes.

Molecular analysis of the CHD7 gene

- *CHD7* mutations were identified in 16 patients: 13 truncating, two missense, and one complete deletion mutations.
- Seven novel mutations (p.A608Gfs*4, p.F2340Ffs*96, p.R157*, p.R2314Nfs*10, p.W983*, p.S1517Lfs*29, p.Q863*, and p.C1643Y) were identified.
- The novel missense variant, p.C1643Y, was predicted to be deleterious by PolyPhen-2 and SIFT.



Red, *CHD7* mutations identified in typical CHARGE syndrome;
Blue, *CHD7* mutations identified in partial/incomplete CHARGE syndrome;
Green, *CHD7* mutations identified in atypical CHARGE syndrome.

Fig. 1. CHD7 protein domains and positions of mutations identified in CHARGE syndrome. Most mutations identified in CHARGE syndrome are nonsense or frameshift. BRK, Brahma and Kismet domain; CD, chromodomain; DEXHc, DEAD-like helicase superfamily including an ATP-binding domain; NLS, nuclear localization signal.

Growth

- Mean height- and weight-SDS were -2.47 ± 1.19 and -2.45 ± 1.84 respectively.
- Of these, short stature of less than -2 SDS was apparent in 13 patients (56.5%).
- Six of 11 (54.5%) typical CHARGE, one of two (50%) partial/incomplete CHARGE, and five of 10 (50%) atypical CHARGE patients were regarded as short stature.
- A female with typical CHARGE syndrome was confirmed to have GH deficiency by L-dopa and insulin tolerance tests at the age of 7.8 years. Serum IGF-1 and IGFBP-3 levels were 5 ng/mL and 956 ng/mL, respectively. She was previously diagnosed with hypothyroidism at age 6.7 years and has been treated with levothyroxine. However, brain MRI did not show abnormalities in the hypothalamic-pituitary region.
- In the remaining 12 patients with short stature, serum IGF-1 and IGFBP-3 levels were normal or low-normal range.

Hypogonadotropic hypogonadism

- Micropenis was found in 13 of 15 boys (86.7%), 8 of whom had unilateral or bilateral cryptorchidism.
- Hyposmia was documented in a female with hypogonadotropic hypogonadism by smell identification test (6/12).
- Two females with typical CHARGE and one male with partial/incomplete CHARGE syndrome were diagnosed with hypogonadotropic hypogonadism during adolescents and subsequently have been under treatment with sex hormone. LH responses to GnRH stimulation were prepubertal pattern.

Table 2. Endocrine characteristics of CHARGE patients with hypogonadotropic hypogonadism

Age at evaluation	Sex	Height -SDS	LH, mIU/mL		FSH, mIU/mL		Testosterone (male) or Estradiol (female)	Bone age
			Basal	Peak	Basal	Peak		
18.6 yrs	F	-1.78	0.89	1.3	0.31	3.8	13.1 pg/mL	13 yrs
15.1 yrs	M	-1.43	1.3	5.2	1.2	4.5	0.06 ng/mL	14 yrs
13 yrs	F	-3.23	3.1	2.8	0.19	1.6	10.0 pg/mL	11 yrs

Thyroid function

- Primary hypothyroidism was found in a 6.7-year-old female and has been treated with levothyroxine. She , however, brain MRI did not show abnormalities in the hypothalamic-pituitary region.

Conclusions

- Hypogonadotropic hypogonadism has been reported as an endocrine defect in CHARGE syndrome.
- However, endocrinological evaluation for GH secretion and thyroid function as well as hypogonadism are necessary in patients with CHARGE syndrome.
- As the ages of the patients in the present study were not in the range that would provide useful information concerning gonadotropin secretion, long-term serial follow-up is needed to assess endocrine functions in patients with CHARGE syndrome.

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Disclosure statement

The authors have nothing to disclose.

55ESPE 710--P2

Endocrinology and Multisystemic Diseases

Jin-Ho Choi

DOI: 10.3252/pso.eu.55ESPE.2016

Poster presented at: ESPE 2016 PARIS