Endocrine dysfunctions in children with CHARGE syndrome
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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 hypothryroidism in patients with CHARGE syndrome.
- Clinical features and endocrine functions were evaluated by retrospective chart review.

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

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
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<tbody>
<tr>
<td>Coloboma, choanal atresia</td>
<td>Rhombencephalic dysfunction</td>
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<tr>
<td>Hypoplastic semicircular canals</td>
<td>Abnormal external or middle ear</td>
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<td></td>
<td>Mental retardation</td>
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<tr>
<td></td>
<td>Hypothalamic-pituitary dysfunction</td>
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<td></td>
<td>Malformation of mediastinal organs (heart and esophagus)</td>
</tr>
</tbody>
</table>

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

- All coding exons (2-38) and exon-intron boundaries of the CHD7 gene 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.
- The novel missense variant, p.C1643Y, was predicted to be deleterious by PolyPhen-2 and SIFT.

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 six (50%) atypical CHARGE patients were regarded as short stature.

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

<table>
<thead>
<tr>
<th>Age at evaluation</th>
<th>Sex</th>
<th>Height-SDS</th>
<th>LH, mIU/mL</th>
<th>FSH, mIU/mL</th>
<th>Testosterone (male)</th>
<th>Estradiol (female)</th>
<th>Bone age</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.6 yrs</td>
<td>F</td>
<td>-2.76</td>
<td>1.8</td>
<td>3.0</td>
<td>1.3</td>
<td>0.5</td>
<td>14 yrs</td>
</tr>
<tr>
<td>15.1 yrs</td>
<td>F</td>
<td>-2.76</td>
<td>1.8</td>
<td>3.0</td>
<td>1.3</td>
<td>0.5</td>
<td>11 yrs</td>
</tr>
<tr>
<td>13 yrs</td>
<td>F</td>
<td>-2.76</td>
<td>1.8</td>
<td>3.0</td>
<td>1.3</td>
<td>0.5</td>
<td>8 yrs</td>
</tr>
</tbody>
</table>

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 hypotalamic-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.

References

Disclosure statement
The authors have nothing to disclose.