A NOVEL COMPOUND HETEROZYGOUS MUTATION IN CYP19A1 RESULTING IN AROMATASE DEFICIENCY WITH NORMAL GONADOTROPIN LEVELS AND OVARIAN TISSUE

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Introduction

- Aromatase deficiency leading to virilization in mother and female fetuses during pregnancy is a rare disease.
- It is characterized by impaired estrogen production, increased gonadotropins, and ovarian cysts.
- Herein, we report a clinical phenotype of a virilized female due to a novel compound heterozygous mutation in CYP19A1.

A 4-month-old ♀

- She was referred due to cliteromegaly.
- Medical history;
  - She was born with a birthweight of 2710 gr at 35th week of gestation.
  - Her clitoris size had regressed after birth.
  - The parents were no relatives.
  - Her mother had developed acne, hair loss, voice change, and hirsutism during pregnancy.
- The physical examination;
  - Her weight was 6.8 kg (0.36 SDS),
  - Height was 64 cm (0.48 SDS),
  - Clitoral length was 1 cm, and labia minora was posteriorly fused.
- Laboratory;
  - Gonadotropin levels were normal at the time of admission but increased by the age of 6 months (Table 1).
  - Initial evaluations excluded congenital adrenal hyperplasia.
  - Ultrasonography revealed a normal uterus but no ovarian tissue.

Further investigations

- Karyotype was identified as 46,XX and SRY was negative.
- Laparoscopic evaluation showed normal uterus and ovaries.
- The biopsy specimens from both gonads were histologically consistent with ovarian tissue and the karyotype analysis of this specimens revealed 46,XX.

Genetic analysis and follow-up

- The diagnosis of aromatase deficiency was considered and a previously unidentified compound heterozygote mutation in CYP19A1 [IVS10 + 1 G>A; p.R115Q (c.344 G>A)] was found.
- The parents were carriers: the mother and the father have heterozygous mutations p.R115Q (c.344 G>A), IVS10+1 G>A, respectively.
- In silico analyzes categorized the variant to be pathogenic.
- During the follow-up, the fusion at the posterior of the labium minus was surgically corrected and no ovarian cyst was observed with pelvic ultrasonography until now.

Hormonal follow-up (Table 1)

<table>
<thead>
<tr>
<th></th>
<th>16th day</th>
<th>4th month</th>
<th>6th Month</th>
<th>8th Month</th>
<th>11th month</th>
<th>17th month</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (mIU/mL)</td>
<td>6.4</td>
<td>7.02</td>
<td>36.3</td>
<td>18.7</td>
<td>27.9</td>
<td>75.1</td>
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<tr>
<td>LH (mIU/mL)</td>
<td>0.53</td>
<td>0.97</td>
<td>4.36</td>
<td>1.27</td>
<td>0.77</td>
<td>15.64</td>
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<tr>
<td>Estradiol(ng/mL)</td>
<td>5.0</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>&lt;20</td>
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<tr>
<td>T. testosterone</td>
<td>78</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Conclusion

- Aromatase deficiency should also be considered even if the initial FSH and LH levels are normal and ovarian cysts are lacking.