Heterozygous CYP11A1 mutation associated with 46XY Disorder of Sex Differentiation and mild Adrenal Insufficiency

Philippa Bowen¹, Nicky Nicolls ¹, Dinesh Giri¹

¹Department of Paediatric Endocrinology, Bristol Royal Hospital for Children, United Kingdom

The authors declare no conflicts of interest

P450scce enzyme deficiency

- Is a rare disorder
- Presents as primary adrenal insufficiency with varying degrees of DSD in 46XY individuals
- Genetics: typically due to biallelic loss of function variants in CYP11A1, either homozygous or compound heterozygous mutations

Clinical case

- Preterm infant (36 weeks gestation)
- Birthweight 2.9 kg
- Non-consanguineous parents
- Hypoglycaemia on day 1 of life that quickly resolved
- Atypical genitalia noted at birth, raising concerns of a possible disorder of sex development; perineal hypospadias, chordee and cryptorchidism

Table 1: Initial investigations from clinical case

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotype</td>
<td>46XY</td>
</tr>
<tr>
<td>USS Pelvis</td>
<td>No mullerian structures Testes in inguinal canal bilaterally</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Stable</td>
</tr>
<tr>
<td>Hypoglycaemia screen</td>
<td>Inappropriately raised plasma insulin level at time of hypoglycaemia</td>
</tr>
<tr>
<td>17 Hydroxyprogesterone</td>
<td>Normal</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Normal</td>
</tr>
<tr>
<td>Renin</td>
<td>Normal</td>
</tr>
<tr>
<td>Short synacthen test</td>
<td>Suboptimal (peak cortisol 397nmol/l)</td>
</tr>
</tbody>
</table>

46XY DSD gene panel

- Heterozygous frameshift mutation in CYP11A1 c.835delA p.(Ile279Tyrfs*1)
- Classified as a pathogenic variant
- Recessive state typically causes severe adrenal insufficiency and 46XY sex reversal and have been widely reported
- Heterozygous CYP11A1 mutation contributing to the phenotype are extremely unusual and rare
- In the absence of other explanation, it is possible that the heterozygous CYP11A1 mutation in our patient is contributing to the phenotype of mild adrenal insufficiency and undervirilisation

Conclusion

- Recessive (homozygous and compound heterozygous) CYP11A1 mutations are known to result in severe adrenal insufficiency and DSD in 46XY infants.
- Heterozygous loss of function mutations in CYP11A1, such as that in our patient, can cause mild adrenal insufficiency and undervirilisation in 46XY individuals
- Due to the rarity of such descriptions in the literature, more reported cases and molecular studies might add to the body of evidence

Reference