A Genetic Diagnosis Of Familial Glucocorticoid Deficiency Resulting In Cessation Of Long Term Mineralocorticoid Treatment In Three Siblings

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Background
- Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disorder
- Adrenocorticotropic hormone (ACTH) resistance leads to isolated glucocorticoid deficiency
- Mutations in the gene encoding the ACTH receptor (MC2R) are responsible for around 25% of cases.

Index case
- Female noted to be hyperpigmented at birth.
- At one week of age ACTH level >1200 ng/ml, plasma renin activity (PRA) 11.4pmol/ml/hr, aldosterone 520 pmol/L.
- Adrenal ultrasound scan did not identify left adrenal gland, right adrenal appeared to be normal size.
- Diagnosed with Adrenal Hypoplasia Congenita (AHC), commenced hydrocortisone and fludrocortisone supplementation.
- Investigations revealed persistently elevated ACTH levels often >1250ng/L/hr yet consistently low PRA below 2nmol/L/hr.

Siblings
- Male and female sibling later diagnosed with AHC and commenced hydrocortisone and fludrocortisone supplementation. They similarly had persistently low plasma renin levels.

Genetic analysis
- Genetic testing found homozygous mutation MC2R gene in all 3 siblings resulting in a diagnosis of FGD.
- Extended testing found both parents and number of other family members to be heterozygous for the MC2R gene mutation.

Changes to management
- Fludrocortisone supplementation gradually reduced then stopped. Subsequent blood pressure readings and sodium levels remained within normal limits.
- The index case, who had been taking fludrocortisone for 14 years, had normal ambulatory blood pressure monitoring pre and post withdrawal of mineralocorticoid.

Learning points
- In our family, despite many years of treatment it was possible to withdraw fludrocortisone and thus remove the risk of unnecessary iatrogenic effects such as hypertension.
- A genetic cause should be pursued in all individuals with AHC. In the presence of persistently low or normal PRA levels, a diagnosis of FGD should be considered.

Table 1. Clinical + biochemical features of FGD

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<tr>
<th>Feature</th>
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<tr>
<td>Hyperpigmentation (often persisting despite treatment)</td>
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<td>Absent adrenarche, normal puberty</td>
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<tr>
<td>Hypoglycaemic episodes/recurrent infections</td>
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<td>Markedly raised ACTH levels, low cortisol</td>
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<td>Usually normal renin and aldosterone levels</td>
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<td>Tall stature seen in some cases</td>
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<td>Advanced/dissociated bone age seen in some cases</td>
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