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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
- Adrenocorticotrophic 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.

Figure 1. MC2R Gene encodes for ACTH receptor, thus only production of Glucocorticoids is affected

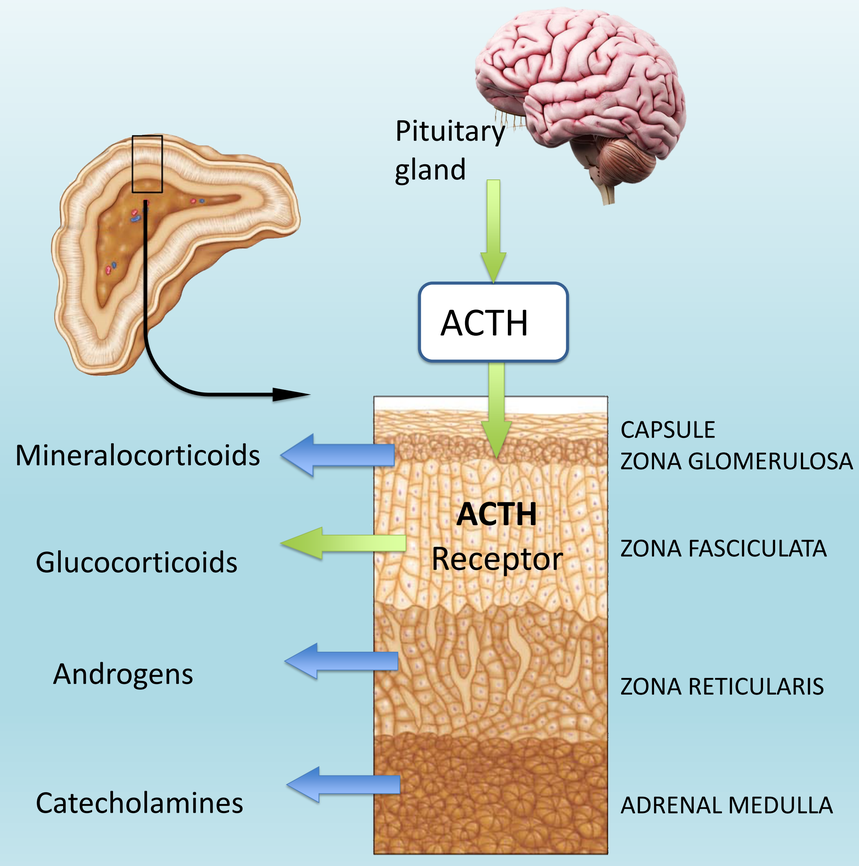

Table 1. Clinical + biochemical features of FGD[1]
Hyperpigmentation (often persisting despite treatment)
Absent adrenarche, normal puberty
Hypoglycaemic episodes/recurrent infections
Markedly raised ACTH levels, low cortisol
Usually normal renin and aldosterone levels
Tall stature seen in some cases
Advanced/dissociated bone age seen in some cases

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.

References [1]Chan L, F, Clark A, J, L, Metherell L, A, Familial Glucocorticoid Deficiency: Advances in the Molecular Understanding of ACTH Action. Horm Res Paediatr 2008;69:75-82

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