An Atypical Case of Non-Classical Congenital Adrenal Hyperplasia

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Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders that impair cortisol biosynthesis. In 95% of cases it is caused by mutations in *CYP21A2,* the gene encoding the adrenal steroid 21-hydroxylase enzyme.[1] Deficiency of 21-hydroxylase leads to an accumulation of cortisol precursors that get diverted to sex hormone biosynthesis.

Consequently there is a wide range of clinical features including adrenal insufficiency, genital ambiguity, infertility, short stature, hypertension and an increased risk of metabolic syndrome.[2]

21-hydroxylase deficiency is classified into 3 subtypes according to clinical severity: classic salt-wasting, classic simple virilising, and non-classic CAH (mild/late onset).[1] Non-classic CAH is one of the most common autosomal recessive disorders in humans and affects approximately 1 in 1,000 individuals.[3]

Case Presentation

We present the case of a 28-year old woman, who presented with menstrual irregularity and hirsutism since menarche, at age 11. She had been treated with the oral contraceptive pill (*Dianettte*) for 12 years, in the context of a diagnosis of polycystic ovarian syndrome, despite BMI of 21 kg/m^2.

Investigations

Blood pressure was 101/66mmHg. Baseline electrolytes showed sodium 140mmol/L, potassium 3.6mmol/L. Testosterone level was 2.1 nmol/L. Short and long synachthen tests confirmed the biochemical diagnosis of CAH (Table 1 and 2). Prolonged oral glucose tolerance test was performed (Table 3), as she complained of hypoglycaemia-like symptoms, confirming hypoglycaemia at 3 hours post-glucose load (glucose 2.1mmol/L) with appropriate spontaneous recovery (glucose 4.1 mmol/L at 300min).

Genetic testing confirmed non-classical CAH due to 21-hydroxylase deficiency. She was heterozygous for c.89C>T and c.841G>T with normal *CYP21A2* copy number.

Table 1: Short synacthen test

Time (min)	Cortisol (nmol/L)	17-hydroxyprogesterone (nmol/L)
0	275	32.5
30	335	173.5
60	371	201.2

Table 2: Long synacthen test

Time (min)	Cortisol (nmol//L)
0	356
30	389
60	488
240	534
360	586
440	815
2880	279

Table 3: Prolonged oral glucose tolerance test

Time (min)	0	30	60	90	120	150	180	210	240	270	300
Glucose (mmol/L)	4	6.6	4.6	3.3	3.7	3.3	2.1	3.2	3.7	3.8	4.1

Follow up

She started Dexamethasone 0.25 mg daily and responded well. Androstenedione levels decreased to 11.4nmol/L. She is still complaining of fatigue in early evening and a cortisol day curve is scheduled to investigate need for a second dose of dexamethasone.

Discussion

Non-classic *CYP21A2* deficiency is one of the most common autosomal recessive diseases. Non-classic CAH and polycystic ovarian syndrome may present similarly as hirsutism is the single most common symptom in patients with non-classic CAH followed by oligomenorrhea and acne.[4]

Despite general correlations, the CYP21A2 deficiency phenotype does not always correlate precisely with the genotype, suggesting that other genes influence the clinical manifestations. Women with late-onset form may be compound heterozygotes (classic mutation and a variant allele) or heterozygotes with two variant alleles, allowing for 20-60% of normal enzymatic activity.[4] This leads to observation of a wide range of phenotypes. Women who are compound heterozygotes for two different CYP21A2 mutations usually have the phenotype associated with the less severe of the two genetic defects.[4]

References

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BES2018 3--EP

Adrenal and steroids

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Poster presented at: SfE BES 2018 19-21 November GLASGOW

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