University College London Hospitals NHS Foundation Trust

Not Always CAH. Urine Steroid Profiling in the Investigation and Diagnosis of Adrenal Causes of Neonatal Hyponatraemia and Failure to Thrive.

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1. PATIENT PRESENTATION

A 1 month old baby boy presented to a local district general hospital with failure to thrive (weight at birth = 3.1 kg, at 28 days = 2.9 kg). The infant was born following an unremarkable pregnancy with nil of note from the antenatal history.

Family History: The parents were non-consanguineous and of Eastern European origin. They had an 18 month old baby daughter who was healthy.

Clinical Observations: Upon clinical examination, the infant had a slightly low, but stable blood pressure for age (65/35 mmHg), but was otherwise normal.

2. INITIAL BIOCHEMICAL INVESTIGATIONS

- Plasma Na^+ 125 mmol/L, K^+ 6.1mmol/L
- Spot urine Na^+ <10 mmol/L
- Blood glucoses 3.5-4.2 mmol/L
- Random plasma cortisols 152, 136 nmol/L

Following Na+ supplementation:

- Plasma Na+ 133 mmol/L
- Plasma K+ 6.3 mmol/L

A short synacthen stimulation test was performed (table 1). Based on these results congenital adrenal hyperplasia (CAH) remained a potential diagnosis and the infant was started on hydrocortisone treatment.

	Cortisol (nmol/L)
Baseline	65
30 mins post-synacthen	286

Table 1: Short synacthen test results

3. ADDITIONAL LABORATORY INVESTIGATIONS

Urine Steroid Profile (USP)

Prior to hydrocortisone treatment, a spot urine sample was taken for USP analysis (figure 1A). The USP did not indicate any variants of CAH but showed elevated corticosterone metabolites in the absence of detectable aldosterone metabolites. The pattern was suggestive of an aldosterone synthase deficiency, specifically corticosterone methyl oxidase type 2 deficiency[1] (figure 2).

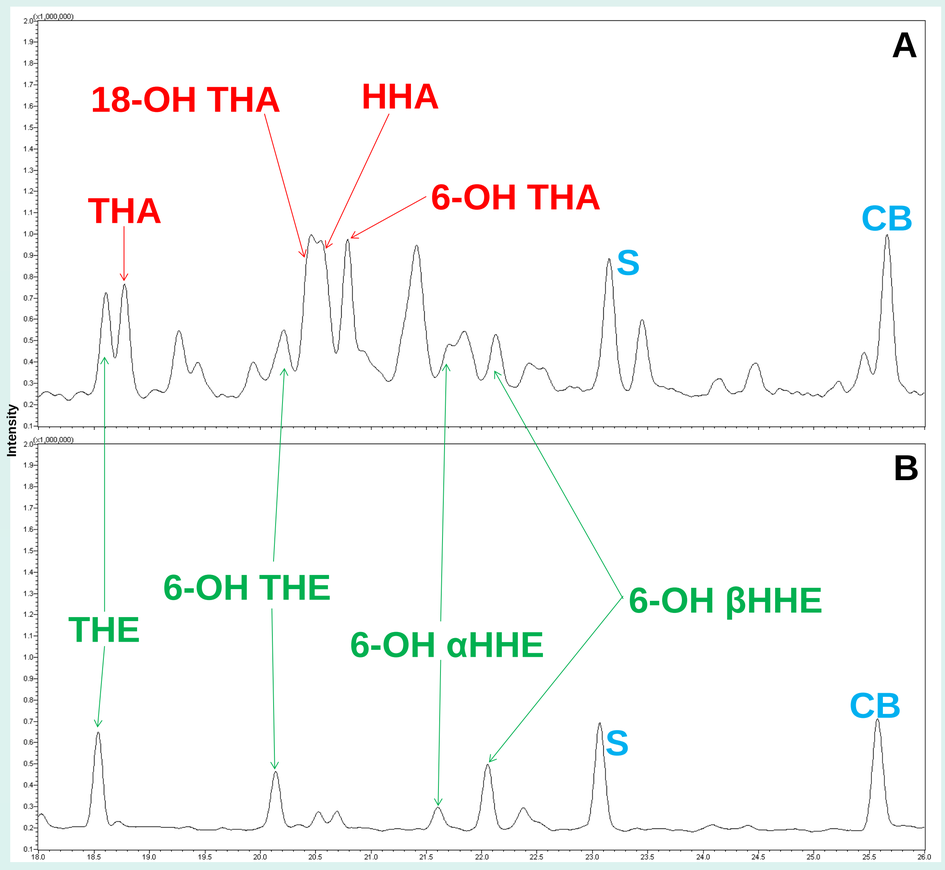

Figure 1: USP chromatograms of the unconjugated/glucuronide fraction from the patient (A) and a normal infant (B). Cortisol metabolites are indicated in green, corticosterone metabolites in red, and the internal standards in blue. THE: tetrahydrocortisone, 6-OH THE: 6-hydroxyTHE, 6-OH αHHE: 6-hydroxy-α-cortolone, 6-OH βHHE: 6-hydroxy-β-cortolone, THA: tetrahydro-11-dehydrocorticosterone, 18-OH THA: 18-hydroxyTHA, HHA: hexahydro-11-dehydrocorticosterone, 6-OH THA: 6-hydroxyTHA, S: stigmasterol, CB: cholesterol butyrate.

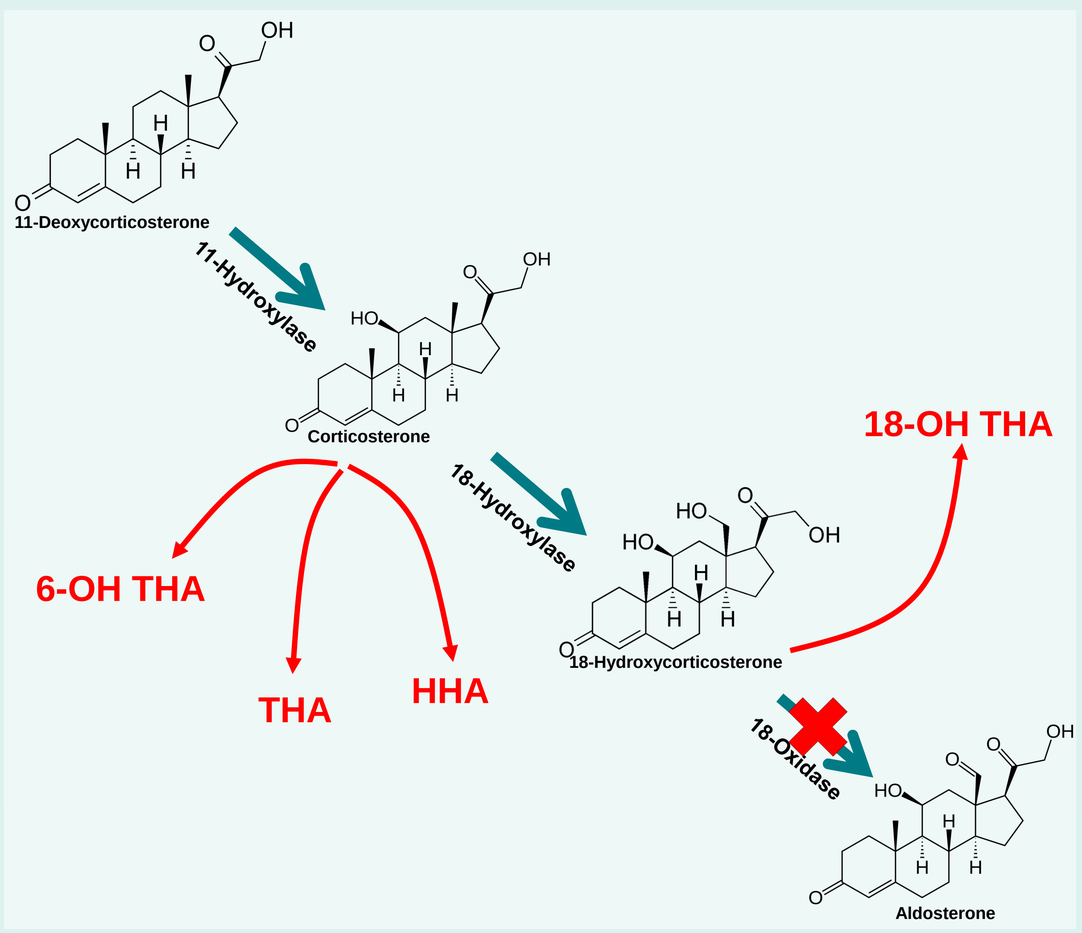

Figure 2: Steroid reactions catalysed by aldosterone synthase. A deficiency in the 18-oxidase activity causes the accumulation of precursor metabolites (18-OH THA, 6-OH THA, THA, HHA) and low/absent product metabolites. Deficiencies in 18-hydroxylase and 11-hydroxylase activities also exist, but produce a different pattern of corticosterone metabolite excretion.

Plasma Aldosterone Concentration and Renin Activity

Radioimmunoassay measurement of plasma aldosterone showed a low-normal concentration of 1040 pmol/L (up to 5000 pmol/L in neonates) with a very raised renin activity of 185 nmol/L/h (neonatal range up to 25 nmol/L/h), which is supportive of an aldosterone synthase defect.

Aldosterone Synthase Whole Gene Sequencing

The *CYP11B2* aldosterone synthase gene was sequenced and showed a c.554C>T substitution (p.Thr185Ile) in exon 3 (figure 3). This is a known pathological change associated with loss of 18-oxidation activity[2].

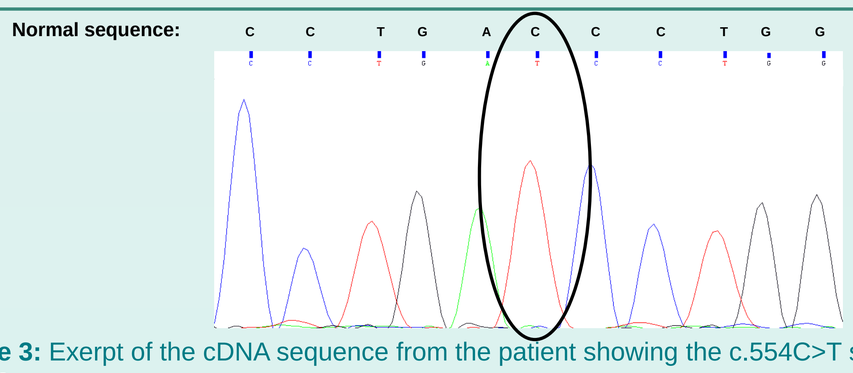

Figure 3: Exerpt of the cDNA sequence from the patient showing the c.554C>T substitution in exon 3.

4. DISCUSSION

The investigation of a young infant presenting with hyponatraemia is challenging, further complicated by the need to obtain sufficient blood samples and prioritise informative tests. Where a steroid disorder is suspected, a USP has great utility since the specimen is easily accessible and the test can identify/exclude a variety of disorders including CAH (incidence ~1 in 18000 U.K. births) and aldosterone synthase defects (rare, unclear incidence). Where urgent samples are involved, analyses can be prioritised with a relatively rapid turnaround time. In this case, the USP diagnosis was made within 2 days of sample receipt, prompting fludrocortisone treatment and reduction of hydrocortisone.

References

1. Honour JW, Dillon MJ, Shackleton CHL (1982). *J Clin Endocrinol Metab* **54**: 325-31
2. Dunlop FM, Crock PA, Montalto J, Funder JW, Curnow KM (2003). *J Clin Endocrinol Metab* **88**: 2518-26