PseudoHypoAldosteronism Type 1 (PHA1): role of urinary steroid profiling (USP) in specific and early diagnosis – lessons in differential diagnosis of PHA1 *vs* PHA2 (renal tract anomaly)

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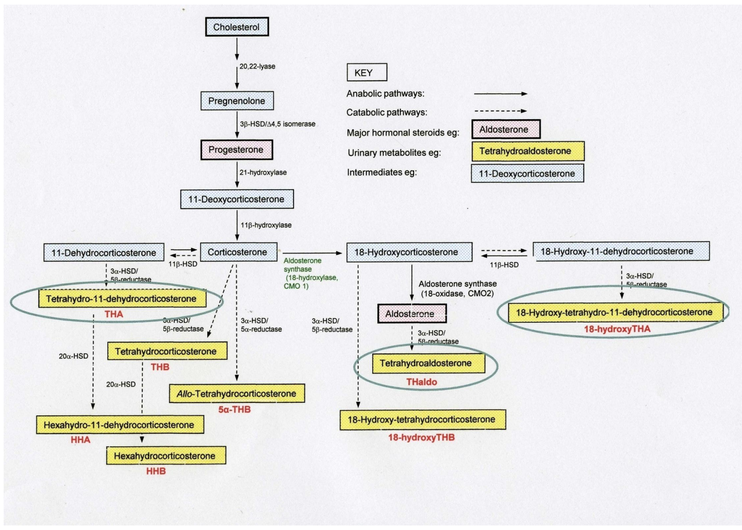
BACKGROUND

PHA1 is a rare disorder of congenital salt loss, resulting from resistance of kidney &/or other tissues to mineralocorticoids, arising from mutations in genes encoding Mineralocorticoid Receptor (MR: *NR3C2*; autosomal dominant), or Epithelial Sodium Channel (ENaC) genes (*SCNN1A/B/G*; autosomal recessive) (see *Riepe FG, 2009* for review). A milder clinical phenotype associates with renal PHA1(*NR3C2*) and shows variable penetrance. Genetic PHA1 may be distinguished from PHA 2ary to urinary tract abnormalities by ***USP, with high levels of aldosterone and mineralocorticoid precursor metabolites characteristic in both conditions (see Steroid anabolic / catabolic pathways Fig.1 adjacent), with additional presence of raised cholesterol peak in PHA2.***

***Figure 1*: Steroid anabolic and catabolic pathways**



OBJECTIVES / METHODS

Case reports: 2 families/ 3 patients.

Urine steroid profiles (USPs) represent Total Ion Current chromatograms of steroids as MO-TMS derivatives, obtained on a Perkin Elmer Clarus 500 single quadrupole GC-MS system.

Pt 1(CH): Female, BWt 3.1kg, 1st child non-consanguinous Caucasian parents. Presented at 3 wks below BWt with serum Na125/ K6.5mmol/l. No hypoglycaemia, Cortisol post-Synacthen, and blood gases: Normal. **USP (age 36 days) diagnostic of PHA1 (see panel)**. *Subsequently available results:*17 OHProg 13.5 nmol/L (Normal for age), Aldosterone 36,000 (N<2000)pmol/L, PRA 61(N<3pmol/ml/hr). Ultrasound Renal tract normal.Stabilised with oral NaCl supps after IV saline treatment. Pt now thriving age 2 ½ yrs on approx. 1mmol/kg/day oral NaCl.
Diagnosis: PHA1, presumed *NR3C2 mutation.* Neither parent has relevant childhood history.

Pt 2 (BJ): Male, newborn sib. Pt 1. BWt 4.1kg, 39 wks, prospectively evaluated for possible PHA1, even though parental history negative. Day1&2 serum U/Es **and USP (day 2 see panel) were Normal.** Day7 serum U/Es Na136/K5.3mmol/L **but USP diagnostic of PHA1 (see panel)**. Day15 reviewed with newly available USP result: Wt loss to 3.88kg, but serum electrolytes remained Normal: Na139/K4.2mmol/L => started oral NaCl supps 5mmol/l/kg/day; Subsequent available serum **Aldosterone 3670pmol/L(N<800) / Renin 282mU/L(N<60).** Clinically well since on same NaCl supps. First review of Aldo / PRA at age 3 months: **both Normal (Aldo 275 / Renin 55 mU/L).** Age 18 mths well.

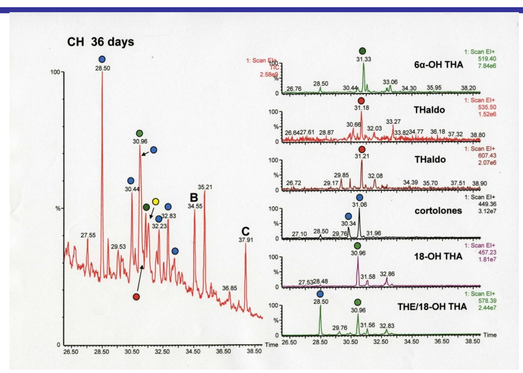
Pt 3 (EA): Female, Born 36wks, Romanian/Indian parents. Em LSCS for prolonged rupture membranes (PROM). Neonatal "collapse" age 14hrs. Presumed sepsis and treated with antibiotics. No definite infection found. Discharged without firm diagnosis. Readmitted with 7% wt loss at 12 days; serum Na132 / K 6.3mmol/L. No hypoglycaemia . Initially considered diagnosis of ***? PHA2 vs PHA1*** in view of maternal PROM and possible sepsis (even though neither maternal nor neonatal significant infection proven) ***and lack of virilisation.*** Cortisol response to Synacthen 993 nmol/L , 17 OHP 4.2 nmol/L; ACTH 15 ng/ml), Renal tract USS and urine micro /culture normal.
Treatment: further empirical antibiotic treatment: =>feeding improved and Na/K normalised. Patient discharged after 1 week, pending Outpatient Endocrine review with outstanding Aldosterone/PRA and USP results. Patient was readmitted Day 22 with further salt-wasting crisis (Na 129 / K 7.7). **Initial Aldo >4000 pmol/L, Renin 4418 (N<60) mU/L & USP result (Day 12) then available, consistent with diagnosis *of either PHA1 or PHA2 as slight increase in cholesterol in addition to raised Aldosterone related metabolites*. USP: PT 120 days is presented to show a typical markedly elevated Cholesterol peak in a male patient presenting with PHA2). USP Day 23 subsequently showed lower cholesterol and thus considered more supportive of diagnosis PHA1.** Empirical treatment with Fludrocortisone (50 mcg/day) and NaCl supplements (4 mmol/kg/day) was sufficient to stabilise clinically and ***subsequen*t USP more supportive of PHA1 with lower cholesterol peak and NO evidence urinary infection**. Fludrocortisone withdrawn during infancy and persistently raised Aldosterone (>3000 pmo/L) consistent with PHA1. Pt continues in good health on 1mmol/kg/day oral NaCl.

Mutation analysis of the NR3C2 gene in progress with both families

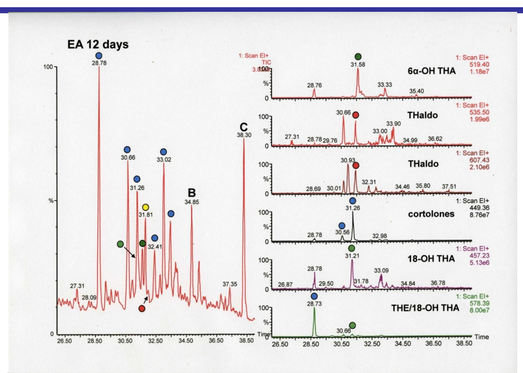
RESULTS

***Figure 2*: GC-MS data of urinary steroids (as MO-TMS derivatives) on patients. An additional USP (PT 120 days) is included to show the characteristic high cholesterol peak associated with PHA2 (which clears after treatment of urinary tract infection or structural abnormality).**
The left hand panels show TIC (Total Ion Current) chromatograms featuring the portion recorded between 26 and 39 minutes, which includes the diagnostic steroid metabolites. B and C are internal standards Stigmasterol and Cholesterol butyrate.
***Blue spots* are Cortisol metabolites** ***Yellow spots* are Cholesterol**
Other colours are identified in the right hand panel, which show extracted Ion Current profiles to highlight the most useful diagnostic metabolites (see Figure 1 above)
Abbreviations:
6a-OH THA: ***6a-hydroxy-TetraHydro-11-dehydrocorticosterone***
THaldo: ***TetraHydroaldosterone (2 ions are shown)***
18-OH THA: ***18-hydroxy-TetraHydro-11-dehydrocorticosterone (2 ions shown)***
THE: ***TetraHydrocortisone***
Cortolones (20A and 20B epimers are shown in order of elution): these are chosen to provide "signpost markers" for the highlighted metabolites

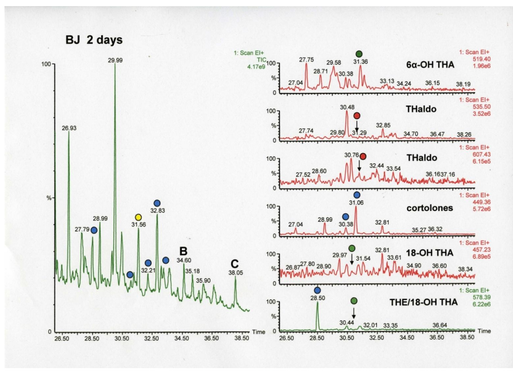
CH 36 days



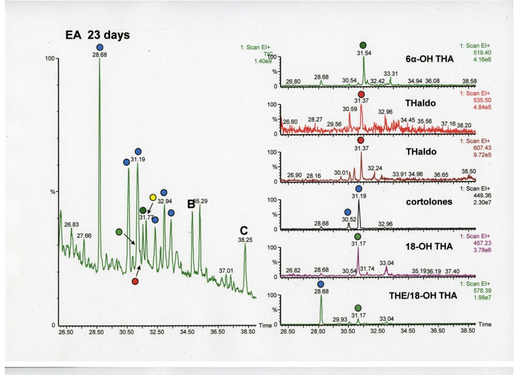
EA 12 days



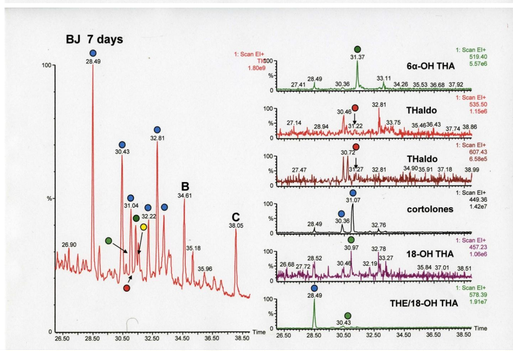
BJ 2 days



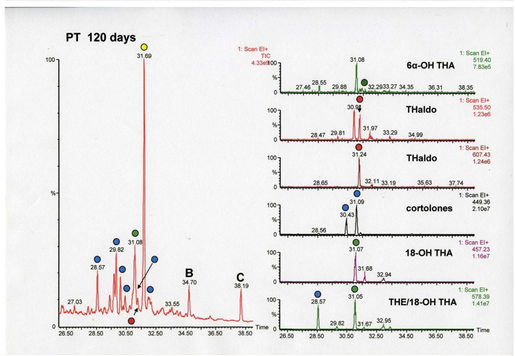
EA 23 days



BJ 7 days



PT 120 days



CONCLUSIONS

*** USP has major role in diagnosis of neonatal salt-wasting disorders**
*** Results may be available before full diagnostic panel of serum parameters**
*** Empirical treatment (Fludro + NaCl) in PHA can successfully manage patients before a specific diagnosis is confirmed**
*** In potential familial cases, USP can provide a non-invasive diagnosis in advance of apparent clinical deterioration**
***The appearance of a significant cholesterol peak in USPs should raise suspicion of PHA2 but full clinical and endocrine assessment is required to support the diagnosis**

Reference

Riepe FG. Clinical and Molecular features of Type 1 Pseudohypoaldosteronism. Horm Res 2009 72: 1-9.