A novel mutation of HSD3beta2 presenting as hypospadias with sat-wasting in a male infant

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Background
Deficiency of the enzyme HSD3beta2 is a rare cause of autosomal recessive primary adrenal insufficiency associated with Disorder of Sexual Development (DSD). Cortisol, aldosterone and other steroid deficiencies occur. Males are typically undervirilised, yet paradoxically some females may be mildly virilised through testosterone production by “backdoor” conversion pathways using iso-enzyme HSD3beta1. Salt-loss, hypoglycaemia and need for mineralocorticoid replacement is variable according to specific defect. As with 21 OH-Def (CYP21), there may be mild non-classic late presenting variants.

Case Presentation

Further investigations (Day 2) for “DSD”:

Results:(1)
Day 2: LH <0.7 / FSH <0.7 IU/L
Day 5: Short Synachten test: 62.5 mcg IV
- Cortisol: 0min 110 /30 min 147 / 60min 109 nmol/L (N > 550)

Genetics: Rapid PCR sex chromosomes XY (result Day 6)
Array CGH Normal Male (result Day 14)

Interpretation: Adrenal insufficiency - ? associated with hypopituitarism in view of microperina and hypospadias. Primary adrenal insufficiency not considered. No discussion with Specialist Paediatric Endocrine Team. Failure to assess pituitary thyroid axis

Management:
Patient started Hydrocortisone 1.25 mg oral 6-hourly Discharged with follow-up: Planned: ~ 1 month neonatal clinic + Paediatric Urology referral for hypospadias

Progress:
Age 26 days referred by GP to AED with h/o 1 day vomiting after feeds. Wt 3520 g; sunken fontanelle / eyes. Plasma Na 108, K 7.1, Urea 11.7 mmol/LCreat 51 micromol/L Urine Na +20 / K 33 mmol/L (Plasma Renin activity 193 mU/L / Aldosterone 240 ng/L)

Management:
IV Saline 0.9% resusc. bolus then 100ml/kg /day IV Hydrocortisone 6 hrly + Ca gluconate; Nebulised salbutamol Convert to oral hydrocortisone 2.3 mg x 3 /day within 48 hrs. Add Fluadrocortisone + oral NaCl 30% supps. ~ 5mmol/kg/day (1 dose / feed)

Methods & Results:(2) Urine steroid profiles

Urine steroid analysis by gas chromatography-mass spectrometry. Chromatograms for the patient and a control subject are compared. Metabolites of the following steroids are shown: cortisol, blue; DHA, green; pregnenolone, purple.

Results:(3) Steroid hormone levels (Collected Day 2):

- Testosterone 15 nmol/L
- Androstenedione >35 nmol/L
- 17 OHPROG 40 nmol/L (Available in 2 weeks later)
- 11DOC 49 nmol/L
- DHEAS / DHT - requested but no results

These results are unexpected in 3βHSD2 deficiency and could represent spurious cross-reactivity of steroids in immunoassays, or “backdoor” conversion of exaggerated DHEA levels by 3βSD1 (Refs 1, 2)

Methods & Results:(4) DNA analysis

DNA was isolated from whole blood HSD3B2 was amplified in 3, non-overlapping fragments followed by Sanger sequencing of individual exons and intron/exon boundaries
- Sequence was compared to reference sequence NC_000018.1. Nomenclature follows HGVS guidelines (www.hgvs.org)
- Exon 2 of HSD3B2 from patient (top) showing homozygosity for an insertion of one nucleotide, c.65dupT. The change leads to a frame shift mutation. p.Leu22Phefs‘27

Parental genetic studies awaited

Progress at 9/2016:
Age 10 months thriving. No further illness. Developmentally normal. Ht / Wt 50th centile. Penile Length straight without significant chordee 3.2 cm erect Rt testis 2ml in scrotal sac. Lt Testis still high at inguinal ring.

Treatment:
Hydrocortisone 2.5 mg oral x 3 / day Fludrocortisone 200 mcg x 1 / day 30% NaCl 5mmol x 5 day with milk/feeds.

Conclusions & Learning points
Urine steroid profile more specific towards definitive diagnosis steroid synthesis disorder than plasma steroid hormone levels

TMStroider analysis better than RIA steroids

Hypospadias NOT a recognised common feature of Hypopituitarism

Disuss DSD case with Endocrine Specialist Team

Life threatening congenital disorders

Acknowledgements:

1) A case of 3β-hydroxysteroid dehydrogenase type II (HSD3B2) deficiency picked up by neonatal screening for 21- hydroxylase deficiency; difficulties and delay in diagnostic diagnosis. Horm Res. 2017 Nov 29;98(5):354-8

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