CYP11A1 (side-chain cleavage enzyme) defect in three brothers causing glucocorticoid and mineralocorticoid deficiency and development of testicular adrenal rest testicular tumour

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Introduction - Aim

- The CYP11A1 gene encodes the cholesterol side-chain cleavage enzyme, P450scC which plays a key role in the initial steps of steroidogenesis.
- CYP11A1 mutations result in a rare form of congenital adrenal hyperplasia with a wide clinical spectrum ranging from severe early onset primary adrenal insufficiency (PAI) in the neonatal period, with 46,XY DSD; to late-onset PAI with normal genitalia.
- Aim: To describe long term outcome in three family members sharing a newly described compound heterozygous CYP11A1 mutation pattern.

Methods

- Initial genetic studies were performed following consent from the parents and children in 2002.
- The following markers were used to determine which X-chromosome had been inherited by each member of the second generation: DXS9899-3 [AH]; DXY-STR50-STR49-STR45-STR44. Four overlapping primer sets covering the 2 exons of the DAX-1 gene were then used to sequence the middle brother's DAX-1 gene: DX1, DX2, DX3 and DX4.
- Subsequent genetic studies were performed in 2016 as part of an initiative to assess the prevalence of CYP11A1 deficiency in PAI using HaloPlex targeted Gene Panel analysis [1].

Family study (see Figure 1)

- The index case II-5 was admitted aged 3.7 years with a prolonged convulsion, initially thought to be febrile in nature (temperature 38.2°C).
- Past medical history:
  - Born at term weighing 2800 g; well at delivery; normal external genitalia.
  - Several presumed “febrile” convulsions during infancy.
  - Admitted with collapse at 18 months, presumed to be septicaemic in cause, with three brief episodes of arm twitching. Admitted to ICU and required ventilation for “shock lung”.
- Family history:
  - Non-consanguineous Scottish family
  - Mother (30 Yrs): History of convulsions as a child, learning disability, chronic alcoholism
  - Father (54 Yrs): Aortic stenosis (valve replacement x 2)
- Siblings:
  - II-1 (10.6 Yrs): History of febrile seizures as a child but normal intelligence and pubertal development
  - II-2 (8.9Yrs): Several convulsions during infancy; developmental delay; special educational needs
  - II-3 (8 Yrs): Frequent convulsions during infancy; hypotonic (tested for Duchenne and fragile X); also attending special school
  - II-4 (6.2 Yrs): Healthy

Examination | Biochemistry
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Deeply pigmented skin | Naa=128 mmol/l (NR:135-145)
Height: 94cm [-1.5 SDS] | K+ = 5.9 mmol/l (NR:3.7-4.8)
Weight: 13.8 kg [-1.13 SDS] | Fasting plasma glucose= 2.8mmol/l
Blood pressure: 90/70 | ACTH= 1089 mU/l (N<20)
Normal prepubertal external genitalia | Basal/peak cortisol after synacthen 174/178 mmol/l
Rest of clinical examination normal | Plasma renin activity= 1209 µU/ml (NR:9-50)

- Assessment in brothers II-2 and II-3 at 8 and 9 years showed that they too were pigmented with normal electrolytes; basal/peak cortisol 339/389 and 278/289 mmol/l
- No history to indicate salt wasting (e.g. vomiting or salt craving) but diet high in salt.

Genetics 1: Glasgow (2002)

- Linkage studies showed that all three brothers had inherited the same critical regions of the maternal X chromosome suggesting an X-linked disorder, but analysis of NR0B1 (DAX-1, adrenal hypoplasia) and ABCD1 (adrenoleukodystrophy) were negative. Triple A syndrome sequencing normal
- Conventional glucocorticoid and mineralocorticoid replacement for unclassified congenital PAI
- Follow-up during childhood and adolescence: All three brothers completed puberty delayed in II-2 and II-3 with G2/G4-5 at 13.1/16.9 and 14.2/17 years.

Summary and conclusions

- Partial CYP11A1 defect is emerging as a surprisingly common cause of previously undiagnosed PAI.
- This kinship demonstrates the importance of precise diagnosis, which could have identified TART as the cause of testicular enlargement thus avoiding orchidectomy in the younger brother.