Investigation of primary adrenal insufficiency (PAI) in children with 46,XY differences in sex development (DSD)

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Objectives: To investigate the prevalence of PAI in children with 46,XY DSD, and to address the role of biochemical testing in diagnosing PAI in 46,XY children presenting with atypical genitalia when no other relevant associated features are present.

Methods:
- Case notes were reviewed of 316 children with 46,XY DSD presenting to a single tertiary centre multidisciplinary team over 26 years.
- Children were identified who had been diagnosed with PAI and treated with steroid replacement.
- Clinical, biochemical, and genetic data were obtained.
- Basal cortisol, standard synacthen-stimulated peak cortisol and incremental rise, and basal ACTH were analysed for those children with PAI, and compared to a 'control' group of children being investigated for 46,XY DSD with normal adrenal function in the first 6 months of life (n=38).
- Assays were performed on an Immulite chemiluminescent immunoassay analyser (cortisol: solid-phase, competitive; ACTH: solid-phase, two-site sequential).
- Key parameters of test performance were calculated.

Results - I

- A total of 10 out of 316 (3.2%) children with 46,XY DSD were diagnosed with PAI.
- Of these, 9 were 46,XY DSD and 1 was 46,XY DS.
- The mean age at diagnosis of PAI was 9 (SD 5.7) months.

Results - II

- Five of these children (1.6%) were first diagnosed with PAI during infancy.
- Three of these 5 children were diagnosed with PAI in the first 6 months of life.

Results - III

- Scatter plots of (A) basal cortisol, standard synacthen-stimulated (B) peak cortisol, (C) incremental cortisol and (D) log₁₀ basal ACTH sampled for the cohort.

Results - IV

- In this cohort, basal ACTH (>60 ng/L) had a sensitivity of 100% and specificity of 84.2%.
- Performance data for basal cortisol (<150 nmol/L) and synacthen-stimulated peak or incremental cortisol are shown in the table below.

Conclusions:
- PAI in 46,XY DSD is an important diagnosis to consider with short- and long-term consequences, but it is uncommon (3.2% of our cohort, over 25 years).
- For those children presenting primarily with DSD/genital differences, basal ACTH is a useful investigation with high sensitivity, if turn-around time is quick.
- Combined basal ACTH (>60 ng/L) AND incremental cortisol (<250 nmol/L) had the best performance in identifying PAI among 46,XY DSD children in this cohort.

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