# 24-hour urinary free cortisol as a screening test for Cushing's syndrome in children

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## Background

Cushing's syndrome (CS) in children remains a challenge to diagnose and exclude. 24 hour urinary free cortisol (UFC) as a diagnostic tool has limitations in adults[1], but might prove effective in children.

## Subjects

We retrospectively reviewed children referred to our centre with suspected CS between 1982-2014. There were 66 patients; 47 with CS (29M) and 19 controls (9M) Controls were patients in whom a diagnosis of CS was suspected but excluded (Tables 1 & 2).

**Table 1. Patient demographics**

| Patient group by diagnosis | Cushing's disease (CD) | Primary pigmented nodular adrenal dysplasia (PPNAD) | Controls |
|---|---|---|---|
| No. of patients (gender) | 39 (25M) | 8 (4M) | 19 (6M) |
| Mean age yrs (range) | 11.7 (5.7-16.9) | 12.9 (10.5-16.9) | 11.5 (4.4-15.7) |

## Assays

UFC was measured by one of three methods: radioassay (RA), immunoassay (IA) or mass spectrography - liquid chromatography (LC-MS). Results were normalised to Body Surface Area (BSA) and expressed as a fraction of the upper limit of the normal range; i.e. result >1 is abnormally high (Table 2).

## Statistical Analysis

Data were analysed by SPSS (version 22; IBM Corp. Armonk, NY). An independent 2 tailed t-test was used to assess the differences between the mean 24-hr UFC values. IA 24-hr UFC results were used in the statistical analyses. The diagnostic accuracy was shown by the AUC values from receiver operating characteristic (ROC) analysis performed against the control group. The results of ROC analyses were classified according to the AUC values as fail (AUC=0.50-0.59), poor (0.60-0.69), moderate (0.70-0.79), good (0.80-0.89) and excellent (0.90-1.00). All 24-hr UFC assays were used for the ROC analysis.

**Table 2: UFC Measurements and patient characteristics**

| | | Patients (CS) | Controls |
|---|---|---|---|
| Number of 24-hr collections | | x1 (53%) x2 (30%) x3 (13%) x4 (4%) | x1 (11%)x2 (47%) x3 (31%) x5 (11%) |
| Clinical features | Height SDS | -1.5 (-5.4 to 2.3) | 0.2 (-3.4 to 2.3) |
| | BMI SDS | 2.2 (-0.6 to 9.2) | 3.2 (2.5 to 4.8) |
| | Hirsutism | 59% | 29% |
| | Hypertension | 52% | 5% |
| | Striae | 55% | 42% |
| | Headaches | 55% | 41% |
| Pubertal staging | Pre-pubertal | 3 (3M) | 6 (2M) |
| | Peripubertal | 40 (24M) | 11 (4M) |
| | Post-pubertal | 4 (2M) | 2 (0M) |

## Results

**Diagnostic accuracy (Table 3)**

- 44/47 (90%) CS patients had elevated 24-hr UFC measurements.
- 5 CS patients had false negative results. All had a diagnosis of CD: elevated midnight cortisol, failure of serum cortisol to supress to <50 nmol/l on LDDST, an exaggerated increase in serum cortisol during CRH test and confirmation of central ACTH secretion on BPIPSS. One had periodic CD secondary to a corticotroph macroadenoma.
- All controls (100%) had normal mean 24-hour UFC.
- Two control subjects had a single UFC measurement which was above the upper limit, but both had overall normal mean.

**Table 3. Diagnostic accuracy**

| Sensitivity | Specificity | AUC |
|---|---|---|
| 94%(44/49) | 100% (19/19) | 0.98 ("excellent") |

## 24-hr UFC and clinical signs

- In patients with CD, the mean 24-hr UFC values were higher in males compared to females (P=0.03). There ere no gender differences in the PPNAD and control groups.
- 24-hr UFC levels did not correlate with clinical severity: BMI, height, hirsutism, headaches, striae or hypertension.
- Height SDS was significantly lower in CS compared to control subjects (p < 0.01, 95% CI 0.99-2.48).
- There was no significant difference in BMI SDS between the subjects and controls.

## Conclusions

- **24-hour UFC measurements have excellent diagnostic accuracy for paediatric CS.**
- **24-hr UFC concentrations were higher in male compared to female CD patients.**
- **24-hr UFC levels did not correlate with clinical severity.**
- **Having more than 1 day 24-hr UFC collection increases the diagnostic accuracy and is recommended.**
- **UFC testing is widely available, non-invasive and can be performed at home.**

[1]Alexandraki KI et al. Is Urinary free cortisol of value in diagnosis of Cushing's syndrome? Curr Opin Diabetes Obes 2011 18(4): 259-63

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