Backdoor Pathway hormones and 11-oxygenated Androgens are elevated in Patients with 21-hydroxylase deficiency

**INTRODUCTION**

Patients with 21-Hydroxylase deficiency (21OHD) present increased levels of cytochrome P450 21-hydroxylase substrates, like progesterone and 17α-hydroxyprogesterone (17OHP).

Previous studies could show that these hormones are involved in the production of androgens via the backdoor pathway.

As a second source of androgens, 11-oxy-androgens derived from the human adrenal glands are recognized as being major androgens. Specifically, 11-oxyandrogens are active androgens in many patients with 21-hydroxylase deficiency.

**AIM**

- develop a reliable LC-MS/MS method for the determination of this "androgen profile"
- measure this in 21OHD patients

**METHOD**

**Patients:**
- Ethical committee vote of the Christian Albrechts University of Kiel, Germany (file number D531/16).
- 56 treatment-naive 21-OHD patients (25 males, 31 females, aged 0-19 years) and age, sex-matched controls

**LC-MS/MS:**
- 5α-pregnan-3α,17α-diol-20-one (pdiol)
- androstanediol
- androsterone
- dihydrotestosterone (DHT)
- Androstenedione
- Testosterone
- 11-ketotestosterone (11KT)
- 11-ketoandrostenedione (11kA4)
- 11-ketodihydrotestosterone (11KDHT)

All children were separated by age:
- newborn children < 25 days and all other children > 25 days, showed in the left and right parts of figures 1-3, respectively.

**21OHD patients** were separated by the 17OHP value according to Speiser et al 2018:
- **Group 1** basal 17OHP > 30 nmol/L, 23 males; 16 females:
  - **Group 2** basal 17 OHP < 30 nmol/L, Cosyntropin stimulation test or molecular genetic analysis was used to confirm the diagnosis in these patients, 3 males, 15 females.
- **Group 3** reference cohort, 23 males, 33 females.

Significantly higher concentrations were found for all 21-OHD patients were found in:
- classical pathway: androstenedione (p<0.001, respectively)
- Backdoor Pathway: pdiol, androsterone (p<0.001, respectively)

In 21OHD patients we revealed a strong correlation between the basal 17OHP value and different androgens:
- Classical Pathway: androstenedione (r=-0.78, p<0.001), testosterone (r=-0.83, p<0.001), DHT (r=-0.73, p=0.001)
- Backdoor Pathway: pdiol (r=-0.61, p=0.001)
- 11-Keto-Androgens: 11KT (r=-0.65, p=0.001)

**CONCLUSIONS**

- We developed a reliable LC-MS/MS assay for an extended “androgen profile”, in 21OHD patients.
- We found a significantly lower mean value of 17OHP in girls than boys in our 21OHD cohort, p <0.001, mean 17OHP in girls: 55 nmol/L and in boys 175 nmol/L.
- In 21OHD patients there is strong correlation between the basal 17OHP value and the level of androgens in the Backdoor Pathway and the 11-Keto-Androgens.

**REFERENCES**


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