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

AE Kulle[1], T. Lamprecht[1], F. Pinto[1], HK Wulf[1], N.Hornig[1], T. Reinehr[2], PM Holterhus[1]

1. University Hospital Schleswig-Holstein, Campus Kiel, Children's Hospital, Department of Paediatrics, Division of Pediatric Endocrinology and Diabetes
2. University of Witten/Herdecke, Vestische Hospital for Children and Adolescents, Datteln

Kiel University
Christian-Albrechts-Universität zu Kiel
Faculty of Medicine

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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 profil"
- measure this in 21OHD patients

METHOD

Patients:

- Ethical committee vote of the Christian Albrechts University of Kiel, Germany (file number D531/16).
- 56 treatment-naïve 21-OHD patients (25 males, 31 females, aged 0-19 years) and age-, sex-matched controls
- a single-center retrospective study of children and adolescents, 2009-2017

LC-MS/MS:

- **5α-pregnane-3α,17α-diol-20-one (pdiol)**
- androstanediol
- androsterone
- dihydrotestosterone (DHT)
- Androstenedione
- Testosterone
- ***11-ketotestosterone (11KT)***
- ***11-ketoandrostenedione (11KA4)***
- ***11-ketodihydrotestosterone (11KDHT)***

RESULTS

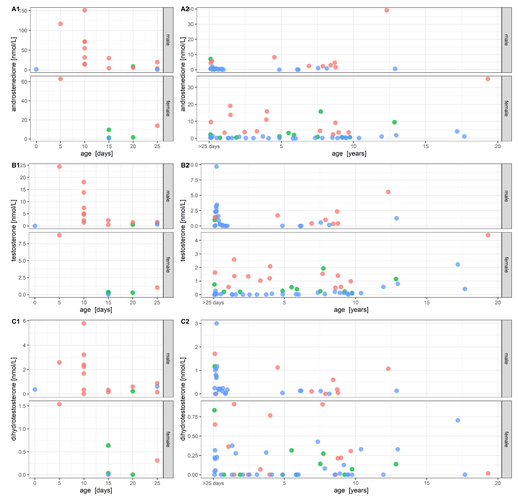

Figure 1 :"classical Pathway" including androstenedione, A1 < 25 days , A2 > 25 days; testosterone, B1 <25 days, B2 > 25 days; dihydrotestosterone, C1 < 25 days, C2 > 25 days

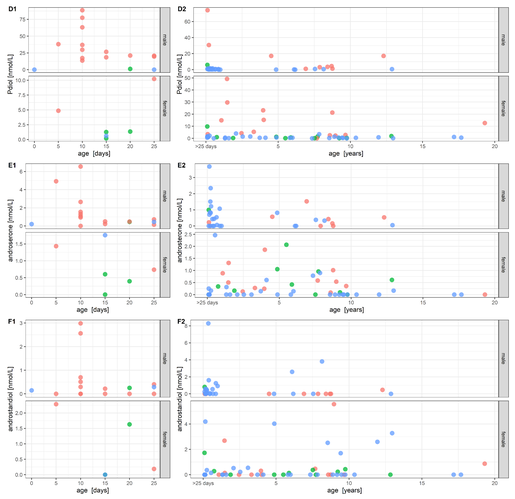

Figure 2. "Backdoorpathway", including Pdiol, D1 <25 days, D2 > 25 days; androsterone E1 <25 days, E2 > 25 days; androstandiol, F1 <25 days, F2 > 25 days

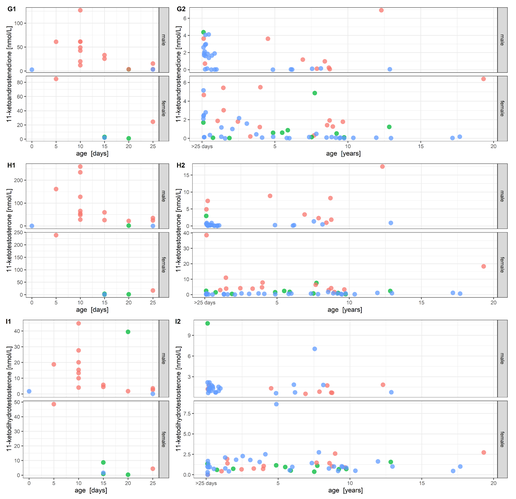

Figure 3. "11-Keto-Androgens", including 11-ketoadrostenedion G1 < 25 days ,G2 > 25 days; 11-ketotesterone, H1 < 25 days , H2 > 25 days; 11-ketodihydotestoerone I1 < 25 days ,I2 > 25 days

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[1]:

- **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.

Signifikantly higher concentrations were found for all **21-OHD patients** were found in:

- classical pathway: androstenedione, testosterone (p<0.001, respectively)
- Backdoor Pathway: **Pdiol**, androsterone (p<0.001, respectively)
- 11-keto-Androgens: ***11KT, 11kA4*** (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 <0.0001[2], mean 17OPH 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

1. Speiser PW, et al. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society* Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*. 2018;103(11):4043-4088. doi:10.1210/jc.2018-01865.
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CONTACT INFORMATION

ePoster Code: P1-9 **Session Name:** Adrenal A
Email: Alexandra.kulle@uksh.de

UKSH UNIVERSITÄTSKLINIKUM Schleswig-Holstein