The Adrenal Steroid Profile in Adolescent Depression: A Valuable Bio-Readout?

R. HIRTZ[1,2], L. LIBUDA[2,3], A. HINNEY[2], M. FÖCKER[4], J. BÜHLMEIER[2], P.-M. HOLTERHUS[5], A. KULLE[5], C. KIEWERT[1], B.P. HAUFFA[1], J. HEBEBRAND[2], C. GRASEMANN[6]

1. Department of Pediatrics II, University of Duisburg-Essen, Essen, Germany
2. Department of Child and Adolescent Psychiatry, University of Duisburg-Essen, Essen, Germany
3. Institute of Nutrition, Consumption, and Health, University Paderborn, Paderborn, Germany
4. Department of Child and Adolescent Psychiatry, University Hospital Münster, Münster, Germany
5. Department of Pediatrics I, University Hospital of Schleswig-Holstein, Kiel, Germany
6. Department of Pediatrics and CeSER, Ruhr-University Bochum, Bochum, Germany

Universitätsmedizin Essen
Universitätsklinikum
Zentrum für Kinder- und Jugendmedizin

ESPE 2021
The 59th Annual Meeting Online
22-26 September 2021

INTRODUCTION

- There is preliminary evidence that **adrenal steroids other than cortisol** may be valuable **biomarkers** for **major depressive disorder** (MDD).
- However, **so far**, studies have been conducted in **adults only**, and conclusions are limited, mainly due to **small sample sizes** (1, 2, 3).

AIM

Against this background, the present study was conducted to investigate whether **selected adrenal steroids** (progesterone, 17-hydroxyprogesterone, 21-deoxycortisol, 11-deoxycortisol, cortisol, cortisone, deoxycorticosterone, corticosterone) serve as **biomarkers** for **adolescent MDD** based on an **adequately powered sample size**.

METHODS

- In **261 depressed adolescents** ($N_{females}$=170), treated at a single psychiatric hospital, serum **adrenal steroids** were determined by **liquid chromatography-tandem mass spectrometry**.
- Findings were compared to that of an **age- and sex-matched reference cohort** (*N*=255) by **nonparametric analysis of variance.**
- Nonparametric **receiver operating characteristics (ROC)** analyses were conducted to evaluate the **diagnostic performance** of **single steroids** and **steroid ratios** to classify depression status.
- **Sensitivity analyses** considered important **confounders** of adrenal functioning, and ROC results were verified by **cross-validation.**

RESULTS

Nonparametric ANOVA

- Compared to the reference cohort, levels of **deoxycorticosterone** and **21-deoxycortisol** were **decreased** (*P* < .001; **Figure 1**).
- **All other** glucocorticoid- and mineralocorticoid-related steroids were **increased** (*P* < .001).

These findings were verified by **sensitivity analyses** considering

- **important confounders** of adrenal functioning (e.g., smoking and psychotropic medication)
- a **subsample** of patients with a **confirmed MDD** diagnosis.

ROC Analysis

- The **corticosterone** to **deoxycorticosterone ratio** evidenced **excellent classification characteristics**, especially in females (AUC: 0.957; sensitivity: 0.902; specificity: 0.891; **Figure 2**)
- This findings held up upon cross-validation

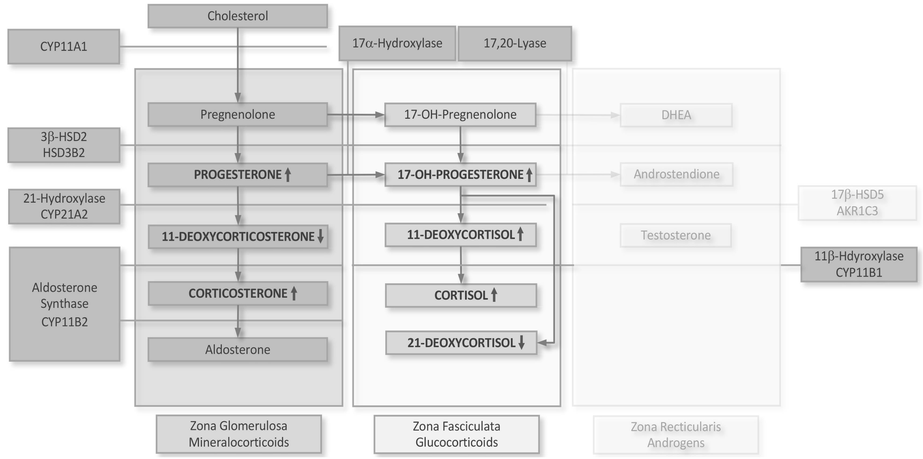

Figure 1. Pathways of steroid hormone synthesis in the adrenal glands, including the involved enzymes and the genes coding these enzymes (boxes surrounding the three adrenal zones). Steroid hormone levels altered in adolescent MDD compared to healthy controls are printed in all capitals and bold type. As androgens were not studied, their synthesis is grayed out. Adapted from Han et al. (4).

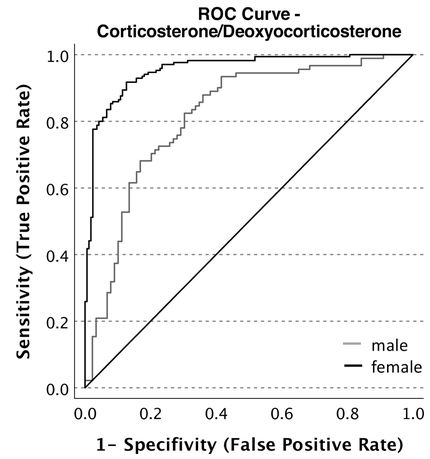

Figure 2. ROC curves for the corticosterone to deoxycorticosterone ratio, separately plotted for males and females.

CONCLUSIONS

The adrenal steroid metabolome **qualifies** as a **bio-readout** reflecting adolescent MDD by a **distinct steroid pattern** that indicates

- **dysfunction** of the **hypothalamus-pituitary-adrenal axis**.
- a **disorder** of the **neuroactive steroid** metabolism.

Moreover, the **corticosterone to deoxycorticosterone** ratio may **prospectively qualify** to contribute to precision medicine in psychiatry by identifying

- those patients who might **benefit from antiglucocorticoid treatment**
- those at **risk for recurrence** when adrenal dysfunction has not resolved.

REFERENCES

1. Holsboer F, Muller OA, Doerr HG, Sippell WG, Stalla GK, Gerken A, et al. ACTH and multisteroid responses to corticotropin-releasing factor in depressive illness: relationship to multisteroid responses after ACTH stimulation and dexamethasone suppression. Psychoneuroendocrinology. 1984;9(2):147-60.
2. Gehris TL, Kathol R, Meller WH, Lopez JF, Jaeckle RS. Multiple steroid hormone levels in depressed patients and normal controls before and after exogenous ACTH. Psychoneuroendocrinology. 1991;16(6):481-97.
3. Holsboer F, Doerr HG, Sippell WG. Dexamethasone suppression of 11-deoxycorticosterone, corticosterone and cortisol in depressed female patients and normal controls. Acta Psychiatr Scand. 1982;66(1):18-25.
4. Han TS, Walker BR, Arlt W, Ross RJ. Treatment and health outcomes in adults with congenital adrenal hyperplasia. Nat Rev Endocrinol. 2014;10(2):115-24.

ACKNOWLEDGEMENTS

R. HIRTZ was supported by the UMEA Clinical Scientist Program by the Faculty of Medicine of the University of Duisburg-Essen and the German Research Foundation (DFG).

CONTACT INFORMATION

RAPHAEL HIRTZ, MD, PhD, Division of Pediatric Endocrinology and Diabetology, Department of Pediatrics II, University Hospital Essen, Hufelandstr. 55, 45147 Essen, Germany.
Tel: + 49 (0)201 723 3371. Fax: + 49 (0)201 723 3308.
Email address: raphael.hirtz@uk-essen.de