Clinical and biochemical phenotype of aldosterone synthase deficiency

Katharina Förtsch[1], Carsten Döing[1], Stefan A. Wudy[2], Michaela F. Hartmann[2], Paul Martin Holterhus[3], Ertan Mayatepek[1], Thomas Meissner[1], Sebastian Kummer[1]

[1]Department of General Pediatrics, Neonatology and Pediatric Cardiology, University Children's Hospital, Duesseldorf, Germany. [2]Steroid Research & Mass Spectrometry Unit, Pediatric Endocrinology, Center of Child and Adolescent Medicine, Justus-Liebig-University, Giessen, Germany [3]Division of Paediatric Endocrinology and Diabetes, Christian-Albrechts-University Kiel and University Hospital Schleswig-Holstein, Kiel, Germany.

Introduction

Biallelic mutations of the *CYP11B2* aldosterone synthase gene cause deficiency of aldosterone synthesis. Patients exhibit isolated deficiency of aldosterone biosynthesis, increased plasma renin activity, increased steroid precursors desoxycorticosterone, corticosterone, and 18-hydroxy-desoxycorticosterone. Clinical symptoms include salt wasting as well as poor growth. Depending on which of the catalytic activities of the aldosterone synthase is predominantly affected, this leads to aldosterone synthase deficiency type 1 or type 2 (cortocosterone methyloxidase [CMO] 1 or 2).

Cases

We report a single-center experience of 7 patients from 5 families diagnosed with aldosterone synthase deficiency, and characterize their biochemical and clinical phenotype as well as the genotype. All of them had characteristic **elevation of 11-desoxy corticosterone and corticosterone** and **inadequately low aldosterone levels.**

All of them presented with **failure to thrive**. In 3 patients this was the main reason for hospital admission. Clinical deterioration with suspected sepsis with electrolyte shift was the reason for hospitalization in 3 other cases, finally turning out as **salt-loosing crisis**. In one case, diagnostic work-up was started due to an affected sibling. Newborn screening for inborn errors of metabolism was normal. Treatment was initiated with **20-25 µg/kg fludrocortisone** daily. Electrolytes and renin levels normalized within a few weeks and all patients showed rapid catch-up growth and weight gain.

Patient (age at diagnosis)	Na^+ (mmol/l)	K^+ (mmol/l)	Renin (ng/l)	Salt wasting crisis	Failure to thrive	18-OH-steroides	Sequencing of CYP11B2 gene	CMO 1 or 2
Patient 1 (6 months)	126	6,7	34600	no	yes	elevated	homozygous p.T185L	2
Patient 2 (0,5 months)	128	7	1940	no	yes	elevated	homozygous p.T185L	2
Patient 3 (4 months)	133	5,6	7725	no	yes	low	homozygous,c.1351C>T(p.L451F)	1
Patient 4 (4 months)	129	6,7	9938	yes	yes	low	homozygous,c.1351C>T (p.L451F)	1
Patient 5 (2 months)	132	5,5	7725	yes	yes	low	n.d.	1
Patient 6 (1 month)	120	6,6	n.d.	yes	yes	elevated	compound heterozygous c.523_525del (p.K175del); c1235 C>T (p.R412P)	2
Patient 7 (7 months)	136	4,8	1917	no	yes	n.d.	homozygous c.554C>T (p.T185I)	n.d.

Tab. 1: Electrolytes, renin- and aldosterone-levels before treatment. Normal levels: renin 9,4-94,5 ng/l, aldosterone 40-310 pg/ml; 11-DOC: 11-desoxycorticosteron; 18-OHB: 18-hydroxy corticosteron

Conclusion

A **defect in mineralocorticoid synthesis** should be part of **the differential diagnoses in every patient with failure to thrive and persistent abnormal serum electrolyte** levels.

Based on our single-centre experience, aldosterone synthase deficiency seems more frequent than expected from established prevalence data, which suggest a extremely rare frequency of <1:1.000.000.

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