Polydipsia, hyponatremia and a biochemical profile of aldosterone synthase deficiency

Christina Reinauer[1], Katharina Förtsch[1], Thomas Meissner[1], Ertan Mayatepek[1], Paul Martin Holterhus[2], Sebastian Kummer[1]

[1]Department of General Pediatrics, Neonatology and Pediatric Cardiology, University Children's Hospital, Düsseldorf, Germany. [2]Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics, Christian-Albrechts-University of Kiel, University Hospital of Schleswig-Holstein, Kiel, Germany

Introduction: Aldosterone is the key regulator of sodium homeostasis. Aldosterone synthase deficiency (ASD) is caused by biallelic inactivating variants of *CYP11B2*, which catalyzes the final three steps of mineralocorticoid synthesis (figure 1). Patients mainly present with failure to thrive and salt wasting in early infancy. Moreover, different factors may cause downregulation of aldosterone synthase and secondary deficiency.

Objective and hypotheses: We present a toddler with polyuria and polydipsia and steroid hormone precursors suggestive of ASD, but normal *CYP11B2* sequencing. We discuss differential diagnoses of ASD.

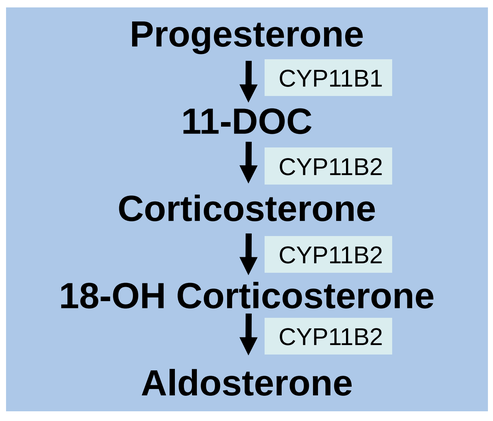

Figure 1:
Aldosterone biosynthesis pathway

Case: A 1.5-year-old German boy was admitted with a first non-febrile status epilepticus with severe hyponatremia of 119 mmol/l. His previous history was uneventful. He was born at term (weight at birth 3580 g, length 52 cm) and did not show any problems in neonatal age or infancy. The boy had thrived well, without vomiting or diarrhea, and had reached developmental milestones adequately. However, parents had noted polyuria and polydipsia (at time of presentation > 2.000 ml/d) since age 3 months.

After a short period of reduced fluid intake during intercurrent illness, he presented with marked hyponatremia of 119 mmol/l with normokalemia (4.4 mmol/l), but no signs of severe dehydration in clinical examination or blood gas analysis (pH 7.29, pCo2 52 mmHg, BE -2 mmol/l). Blood pressure was normal, and urinary sodium excretion was not excessively elevated (93 mmol/l, FeNa 0.85%). There were no signs of SIADH, the brain MRI was normal. Meningitis, systemic and renal infection and heart disease were excluded. A clinical thirst trial later ruled out disorders of vasopressin secretion, with normal copeptin, serum and urine osmolarity after fluid restriction. With calculated infusion therapy, his status rapidly improved.

Aldosterone was detectable but inadequately low considering the context of the severe hyponatremia. The patient showed unusually high levels of corticosterone as a precursor of aldosterone synthesis (ratio >5). After normalization of sodium levels, ACTH stimulation tests were performed: Corticosterone and 11-desoxycorticosterone were markedly elevated and 18-OH-Corticosterone showed an exaggerated response (figure 2). Aldosterone levels were low and did not show any relevant increment after ACTH, displaying the biochemical pattern of an enzyme deficiency in terminal steps of aldosterone synthesis. A good cortisol response and otherwise normal steroid profile ruled out 21-hydroxylase (*CYP21A2*) or *CYP11B1* deficiency.

With fludrocortisone treatment (0.1 mg/day) the boy continued to thrive, however, polydipsia remained. While biochemically there was the clear metabolic fingerprint of aldosterone synthase deficiency, genetically, the diagnosis of ASD could not be confirmed in *CYP11B2* sequencing. Exons and intron-exon borders were investigated by Sanger-sequencing. We only detected a heterozygous common variant in the coding sequence of the *CYP11B2* gene (heterozygous for c.518A>G (p. Lys173Arg)), not explaining the phenotype.

Currently, at age 2.8 years the boy thrives well, even after discontinuing fludrocortisone treatment. The clinical situation is stable, while the biochemical profile of ASD remains. This spontaneous improvement over time is also often observed in ASD, where electrolytes tend to normalize spontaneously from age 3-4 years.

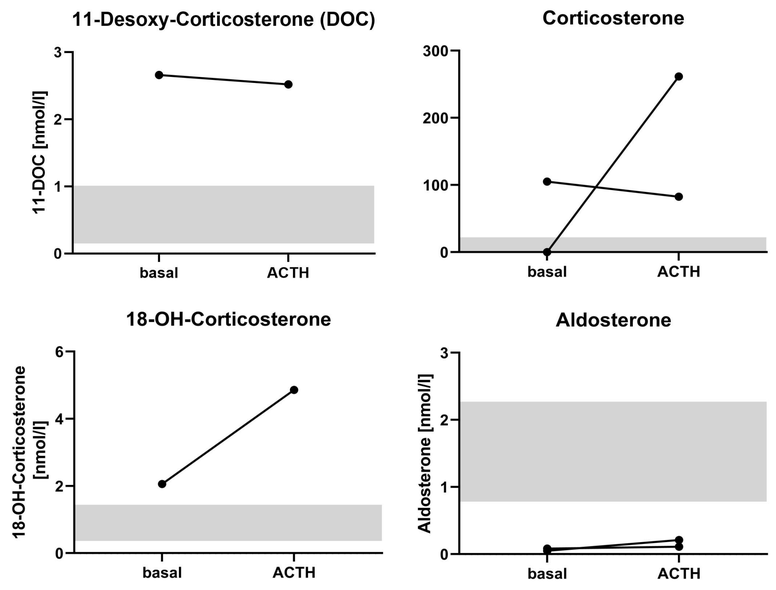

Figure 2: High dose ACTH tests, age adapted normal ranges in grey (corticosterone and aldosterone from repeated ACTH tests)

Discussion:

Differential diagnoses that might cause this partial failure include

- Mutations in non-coding areas / introns.
- Mutations in the promotor region.
- Digenic synergistic mutations affecting genes other than *CYP11B2.*
- It is unclear if a heterozygous deletion of *CYP11B2* may cause a mild but clinically relevant phenotype (undetected by Sanger-sequencing).

Other factors besides the *CYP11B2* gene might influence aldosterone production, for example

- Polydipsia with higher ANP levels might inhibit aldosterone secretion. However, the low aldosterone levels remained after volume restriction.
- Renin levels were high to normal, so in our case hyporeninemic hypoaldosteronism is unlikely.
- Mutations in upstream regulators or other regulatory factors which are currently unknown, e.g.
  - Salt-inducible protein kinase is considered one of the regulators of *CYP11B2* gene expression.
  - *KCNJ5* is important for baseline aldosterone secretion.

Conclusion: Aldosterone synthase deficiency is an important differential diagnosis in isolated hyponatremia in toddlers. However, differential diagnosis can be challenging when diagnosis cannot be confirmed genetically. Several unsolved cases with apparent hypoaldosteronism without *CYP11B2* mutations have been described previously.

Partial phenotypes may only be detected metabolically. The broad spectrum of functionality will be further elucidated in the era of steroid profiles. In our case we assume a partial defect in aldosterone synthesis, with current compensation. The affected genes influencing aldosterone synthesis remain an intriguing puzzle. Next steps in our case might include whole genome sequencing.

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