Lessons from Wolfram Syndrome: Initiation of DDAVP therapy causes Renal Salt Wasting due to elevated ANP levels, rescued by fludrocortisone treatment

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Backgound - Hypothesis

Initiation of DDAVP for untreated diabetes insipidus (DI) causes abrupt volume expansion resulting in particularly high secretion of Atrial Natriuteric Peptide (ANP)[1]. ANP blocks all stimulators of zona glomerulosa steroidogenesis, resulting in secondary mineralocorticoid deficiency and acute hyponatremia, causing renal salt wasting (RSW)[2].

Cases

Two sisters, a 19-year-old girl (A) and a 7-year-old girl (B) with Wolfram Syndrome presented to our pediatric endocrinology clinic with severe polyuria-polydipsia and neurogenic bladder due to never treated DI (3). Both hospitalized, initiated therapy with oral melt preparation of DDAVP at the dose of 120-240 mg x 3/day, under close clinical and biochemical surveillance. Plasma levels of ANP were quantitatively detected by a competitive enzyme immunoassay kit (RayBiotech, Norcross, USA, sensitivity 1.02 pg/ml).

Results

Patient A presented RSW at day 2 after DDAVP initiation. Hyponatremia 123 mmol/L, hyperkalemia 5.7 mmol/L with high natriuresis 120-170 mmol/L occurred, with low plasma renin activity (PRA) 0.94 ng/ml/h (0.5-4.7) and aldosterone 2.26 ng/dl (4-31) and extremely elevated ANP 2359.5 pg/ml (normal < 42). Patient B presented RSW at day 11 after DDAVP initiation. ANP was elevated 1911.5 pg/ml with low PRA 0.78 ng/ml/h and aldosterone 3.46 ng/dl. Both had signs of volume depletion: negative water balance, tachycardia and increased cardiac rate with low blood pressure. Fludrocortisone 100-200 x 2 μg/day controlled natriuresis and restored electrolytes to normal within 48hrs in both patients. Fludrocortisone could be stopped at 1 month in patient B, but ANP levels remained too high 1200-1350 pg/ml, probably due to severe hydronephrosis secondary to grade III bilateral vesicoureteral reflux, in addition to the neurogenic bladder already installed. Patient A still requires - a year after - fludrocortisone at 50 x 2 μg/day with elevated but much lower ANP (250-500 pg/ml).

Figure 1-5. Patient A, evolution of plasma Na and K (1), urine Na (2), urine SG (3), therapy with oral DDAVP and Fludrocortisone (4), ANP levels (5) over a period of 14 months.

Figure 6-10. Patient B, evolution of plasma Na and K (6), urine Na (7), urine SG (8), therapy with oral DDAVP and Fludrocortisone (9), ANP levels (10) over a period of 14 months.

Conclusion

Fludrocortisone treatment rescues otherwise potentially life-threatening hyponatremia due to RSW and the secondary mineralocorticoid deficiency driven by elevated ANP, caused by sudden volume expansion following DDAVP initiation.

1. Mineralocorticoid deficiency in post-operative cerebral salt wasting. Papadimitriou DT et al. J Pediatr Endocrinol Metab. 2007 PMID: 18051934
2. Cerebral Salt Wasting Complicated by Central Diabetes Insipidus and Growth Hormone Deficiency. Papadimitriou DT et al. Indian J Pediatr. 2018 PMID:29455327