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

Kleanthis Kleanthous¹, Eirini Maratou², Dora Syropoulou², Eleni Dermitzaki³, Christina Bothou³, Anastasios Papadimitriou⁴, George Zoupanos⁵, Paraskevi Moutsatsou⁶, Fumihiko Urano⁷, Dimitrios T. Papadimitriou⁸

¹Division of Pediatric Endocrinology, 2nd Department of Pediatrics, Attikon University Hospital, Athens, Greece; ²Department of Clinical Biochemistry, Medical School, National and Kapodistrian University of Athens, Greece; ³3rd Department of Pediatrics, Medical School, National and Kapodistrian University of Athens, Attikon University Hospital, Haidari, Greece; ⁴Division of Pediatric Endocrinology, Athens Medical Center, Athens, Greece; ⁵Division of Endocrinology, Diabetes and Metabolism, Medical Department 1, University Hospital, Goethe University Germany; ⁶Department of Pediatric Urology, Athens Medical Center, Maroussi, Greece; ⁷Washington University School of Medicine, St. Louis, MO, USA

info@pedoendo.gr

No disclosures

Background - Hypothesis
Initiation of DDAVP for untreated diabetes insipidus (DI) causes abrupt volume expansion resulting in particularly high secretion of Atrial Natriuretic Peptide (ANP). 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 1200-1530 pg/ml, probably due to severe hydrenephrosis 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).

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.

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.

1. Mineralocorticoid deficiency in post-operative central salt wasting, Papadimitriou DT et al., Pediatr Endocrinol Metab. 2007 PMID: 18051934