Thyrotoxicosis, nephrogenic syndrome of inappropriate antidiuresis, tall stature and mental retardation caused by a novel GNAS gain of function mutation

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Background: Nephrogenic syndrome of inappropriate antidiuresis (NSIAD) is a very rare clinical condition. Patients suffer from hyponatremia, hypo-osmolality with inappropriately elevated urinary osmolality and undetectable AVP levels. Activating mutations of AVPR2, the vasopressin receptor type 2 (V2R), induce a prolonged signaling of the intracellular cAMP/PKA pathway and cause NSIAD in patients.

Objective and hypotheses: To describe a new phenotype in a patient with symptoms suggestive of increased activity of several GPCRs, a pattern reminiscent of McCune Albright syndrome (MAS), yet with a different phenotype including the phenocopy of the V2R constitutive activation.

Patient: A 4-years old tall girl had persistent hyponatremia (118 to 128 mmol/L) and antidiuresis. Her plasmatic osmolarity was low (260 mosmol/L/kg) while the urinary osmolality was inadequately elevated (1020mOsmol/kg). The AVP level was undetectable. No variant was identified in the AVPR2 gene. She also had symptoms of androgen secretion (mild clitoral enlargement, pubic hair and advanced bone age, slightly elevated testosterone and sDHAd levels). Adrenals were of normal size and shape on the CT-scan. At the age of 5 years, she developed a non-immune thyrotoxicosis. At the age of 6, a café au lait spot appeared on the tight.

Transfection of the mutated S250I-Gsa in Gnas null cells demonstrated a greater accumulation in cAMP compared to the wild-type Gsa (p=0.0004) but a lesser cAMP production than that we observed upon R201-Gsa transfection (the activating mutation responsible for MAS) (p<0.0001).

Conclusion: We describe a novel form of constitutive Gsa activation responsible for NSIAD and thyrotoxicosis.

The authors have nothing to disclose