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

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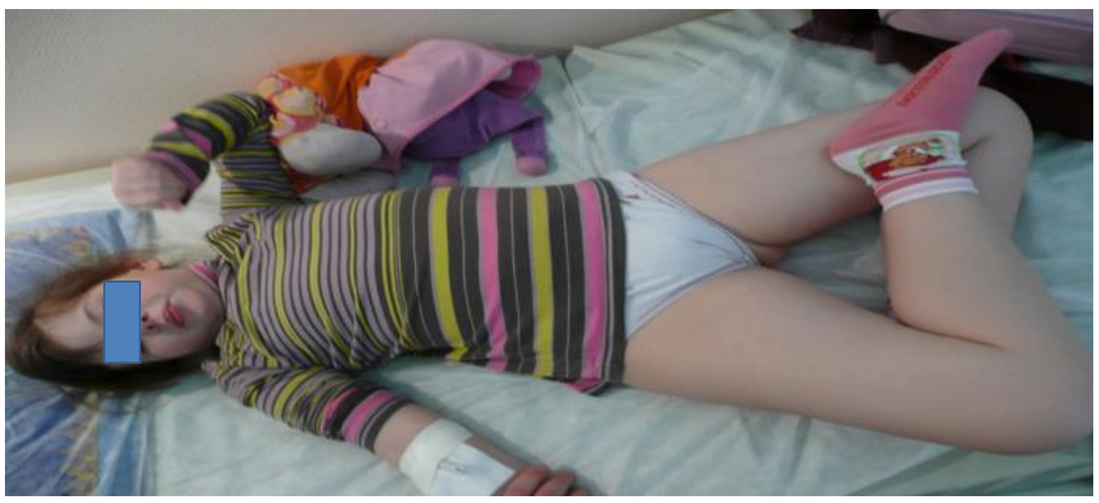
Background: **Nephrogenic syndrome of inappropriate antidiuresis (NSIAD)** is a very rare clinical condition. Patients suffer from hyponatremia, hypo-osmolality with inappropriately elevated urinary osmolality and undetectable AVP levels. Activating mutations of **AVPR2**, the vasopressin receptor type 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 Mc Cune 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/lkg) while the urinary osmolarity 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 sDHA 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.



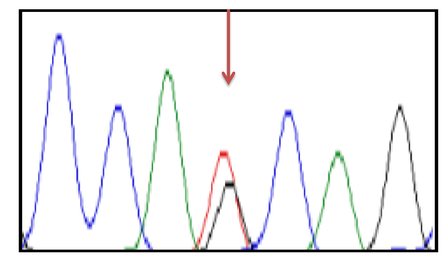
Our tall patient (+3.5 SD) with hyperlaxe joints, when she was five

The authors have nothing to disclose

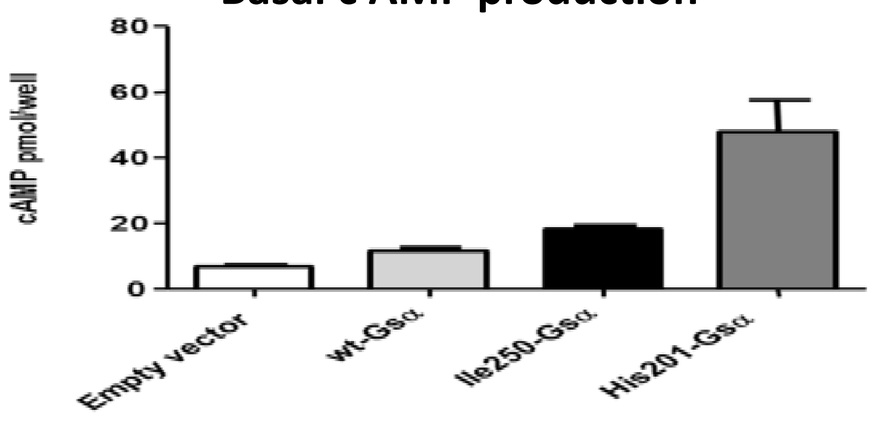
Results: We speculated that the patient could have a constitutional activation of the cAMP/PKA pathway and we searched for mutations in candidate genes downstream of AVPR2 and the TSH receptor. We found a de novo S250I mutation in *GNAS*, encoding the alpha-subunit of the stimulatory G protein (Gsα).

c.749C>T
(S250I)

genomic DNA
exon 10



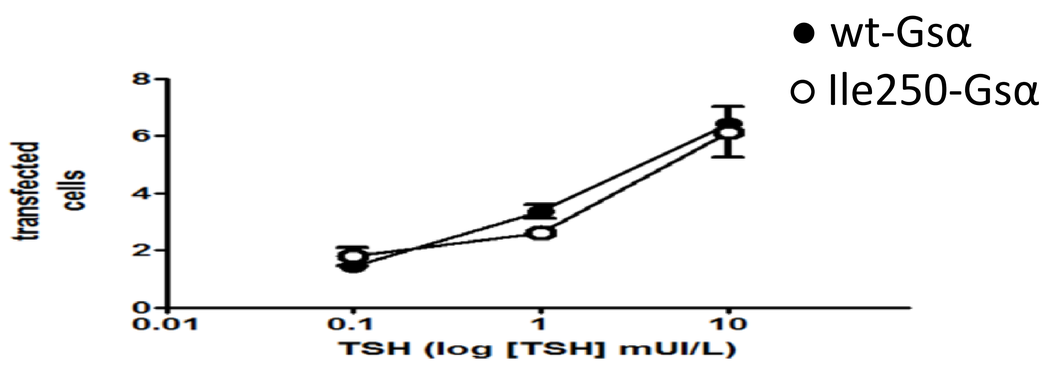
Basal c AMP production



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

AMPc

Stimulated c AMP production



Gnas null cells cotransfected with plasmids encoding the TSH receptor and wt-Gsα or Ile250-Gsα, were submitted to escalating concentration of TSH (0.1, 1 and 10 UI/L). Measured levels of cAMP were normalized to the basal cAMP production obtained through wt-Gsα expression to generate ratios of fold of increase over basal wt-Gsα cAMP *(mean +/- SEM)*. In these experimental conditions, the cAMP accumulation upon TSHR stimulation did not differ between wt-Gsα and Ile250-Gsα transfected cells (p=0.89, paired t-test). **The Ser to Ile substitution in position 250 generates a gain in Gsα constitutive activity, without modifying its agonist-induced cAMP production**

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

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