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Progressive development of PTH resistance in patients with maternal GNAS inactivating mutations

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OBJECTIVES

•Pseudohypoparathyroidism (PHP) type 1A (PHP1A) patients present with parathormone (PTH) resistance, varying degrees of Albright hereditary osteodystrophy (AHO), hypocalcemia and resistance to other hormones including TSH. PHP1A is caused by mutations the *GNAS* gene [(1-2)]. *GNAS* encodes Gsα, the alpha-subunit of the stimulatory G-protein necessary for the proper signaling of the PTH receptor. Clinical diagnosis of PHP1A relies on the discovery of PTH resistance associated with features of AHO. However, patients often do not present with elevated levels of PTH until after the first years of life [(3)].

•The aim of this study is to show the importance of an early diagnosis of PHP1A based on other criteria than PTH resistance.

METHODS

•Retrospective study of 20 patients affected by PHP1a. Inclusion criteria were:

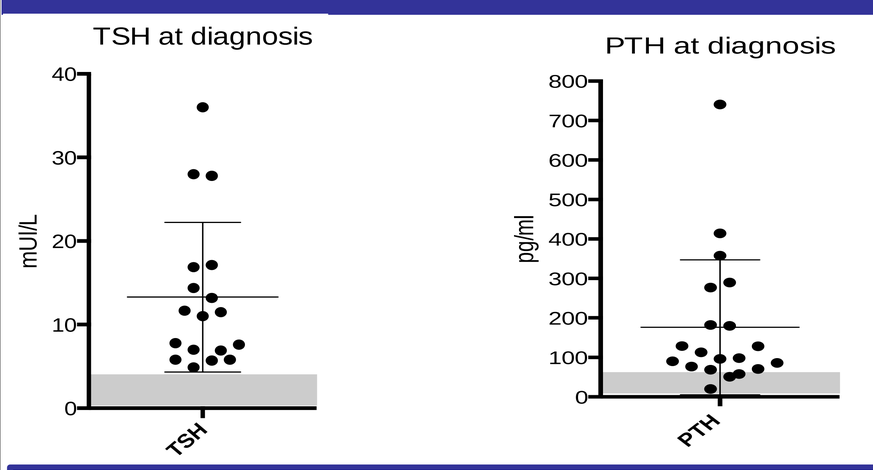
1- mutation in the *GNAS* gene;

2- at least one of the following sign at diagnosis: familial history, ectopic ossification, short stature, obesity, hypocalcemia or brachymetacarpy;

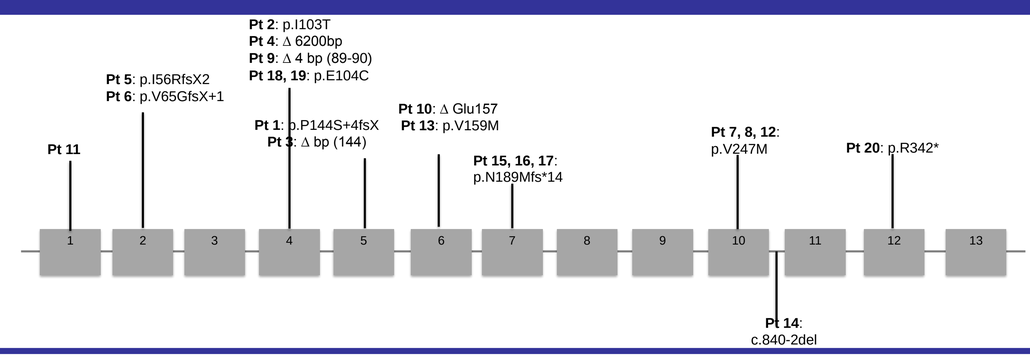
3- have not received calcidiol treatment yet

•We collected measurements of PTH, TSH, calcium and phosphate levels over an average 2 years' follow-up . PTH infusion test was also performed in one patient.

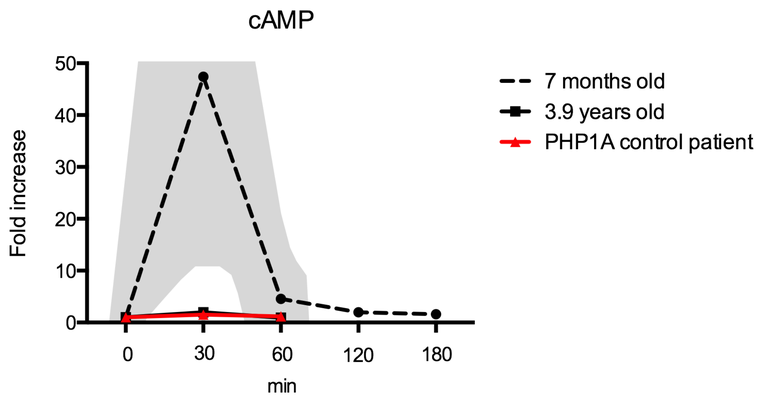
RESULTS



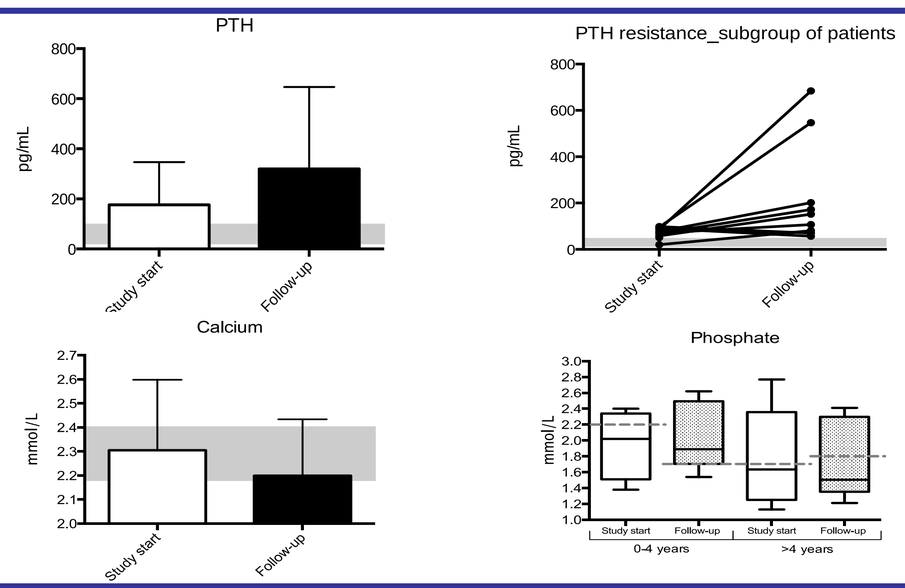
PTH and TSH values at diagnosis. All patients showed elevated level of TSH at diagnosis (left panel) while PTH values for a subgroup of patients (n=10) were normal or subnormal (right panel).



Mutations of the gene GNAS. Patients included in the study presented with mutations spanning all along the GNAS gene and all kind of mutations (frameshift, deletions, insertions, nosense and missense mutations)



PTH infusion test in a patient with a GNAS mutation. Significant rise of urinary cAMP was seen at the age of 7 months (dashed line). A lack of a response, similar to a PHP1A control patient (red line) at the age of 3,9 years (full black line) shows the development of PTH resistance overtime.



Evolution of PTH resistance throughout time. The mean value of PTH significantly increases in all patients (upper panel, left); That increase is more evident in the subgroup of 10 patients with normal or subnormal PTH values at diagnosis (upper panel right). Calcium level significantly decreased and the phosphate level increased while adjusted to the age (lower panel).

CONCLUSIONS

•This work suggest that an early diagnosis of PHP1A patients could be achieved by screening for maternal *GNAS* mutation in the presence of varying degrees of AHO and TSH resistance even in the absence of PTH resistance and hypocalcemia.

•An early diagnosis of PHP1A will permit to start calcidiol treatment at early stages of the disease in order to improve the care and ameliorate the quality of life of PHP1A patients.

References

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No conflict of interest

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