Pseudohypoparathyroidism type Ib: two cases with different clinical presentation.

C. Balsamo[1], F. Baronio[1], A. Marsigli[1], V. Bonifacci[2], G. Mantovani[3], A. Molinaro[4], Harald Jüppner[4], P. Visconti[5], L. Mazzanti[1], A. Balsamo[1]

[1]Pediatric Endocrinology Unit, S.Orsola-Malpighi Hospital, Department of Pediatrics, University of Bologna, Italy, [2]Department of Pediatrics, University of Ferrara,Italy, [3] Department of Clinical and Community Sciences, University of Milan, Italy, [4]Endocrine Unit, Harvard Medical School and Massachussets General Hospital, Boston ,MA,USA, [5] Infantile Neuropsichiatry Unit-Maggiore Hospital. Bologna, Italy

Disclosure Statement: The authors have nothing to disclose

Background: Sporadic pseudohypoparathyroidism type Ib (spor-PHP-Ib) is caused by *GNAS* methylation alterations with loss of imprinting at the exon A/B Differentially Methylated Region (DMR), without genetic deletions disrupting the STX16 ICR. These patients classically display hormone resistance limited to PTH and TSH with no Albright Hereditary Osteodistrophy (AHO).

Objective: we describe two cases with the same imprinting methylation defect, but different clinical presentation.

Patient 1: ♀ 10/05/2005

Firstly evaluated for Slipped Capital Femoral Epiphysis (SCFE) at 6 years of age and severe osteoporosis. She showed high PTH levels, normal calcium levels, but hyperphosphatemia. TSH was in normal range.

Patient 1	at start therapy	after 6 months	after 12 months	after 18 months
PTH (15-65 ng/ml)	445	296	111	34
Serum calcium (8.5-10.5 mg/dl)	9	9	10.5	10.5
Serum phosphate (3.7-5.8 mg/dl)	6.5	5.8	5.2	4.8
Calcitriol supplementation (ng/kg/d)	10	20	20	20
calcium supplementation (mg/kg/d)	10	20	20	20

Patient 2: ♂ 13/08/2003

First evaluation for suspicious neurologic disease (9 years and 10 months) presenting with vertigo, eye lateral deviation and diplopia. He underwent brain computed tomography that did not show cerebral infarction or expansive lesion, but basal ganglia calcifications. He showed high PTH levels, severe hypocalcemia and hyperphosphatemia. TSH levels were slightly elevated.

Patient 2	at start therapy	After 6 Months	after 9 months
PTH (15-65 ng/ml)	369	89	31
Serum calcium (8.5-10.5 mg/dl)	6.7	9.4	10.1
Serum phosphate (3.7-5.8 mg/dl)	9.1	5.2	4.6
TSH (0.27-4.2 mcU/ml)	5.6	6.7	6.5
Calcitriol supplementation (ng/kg/d)	18	25	25
calcium supplementation (mg/kg/d)	35	33	33

Both cases did not show AHO.

Therefore PHP-Ib was suspected and confirmed by molecular analysis

Mutation analysis

gain of methylation at NESP55 and loss of methylation at A/B, XLαs, and antisense (GNAS-AS1) promoter

Our patients share the same methylation abnormality on the *GNAS* gene locus, however they differ in phenotype expression.

Hypothesis:

1.our patients probably have different bone sensitivity to PTH;

2.prolonged (unrecognized) hypocalcemia led to basal ganglia calcification in case 2;

3.higher bone PTH sensitivity led to normal calcium serum levels, with secondary osteoporosis and SCFE in case 1;

4.interestingly all cases with PHP Ib with SCFE reported by literature are females.

Conclusions:

Our two cases differed in clinical features, while showing comparable genotypes.

They seem to confirm that the long-term effects of elevated PTH on bone are still controversial in these patients and they may be dependent on other factors