What Lies beneath: An Enigma of Missed Opportunities- Calcium Problem

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Background

Pseudo hypoparathyroidism (PHP) is a genetic disorder characterized by parathyroid hormone (PTH) resistance and associated with hypocalcaemia and hyperphosphatemia. There are several types of PHP (type Ia, Ib, Ic, type II), based on the genetic mutation of GNAS gene and phenomenon of Genomic Imprinting. Patients with Pseudo hypoparathyroidism (Pseudo PHP) may have variable phenotypic presentation and can pose difficulties in making early diagnosis. It is important to consider this disorder in the evaluation of patients presenting with persistent hypocalcemia.

Methods

Three siblings presenting to different clinic settings with hypocalcaemia and varying phenotypes. The Index case (Case 3), presented acutely with hypocalcaemic tetany and high PTH. Subsequently other two siblings were diagnosed with PTH resistance.

Results

X-Rays left wrist: The fourth metacarpal bone appear marginally shorter, raising suspicions of pseudohypoparathyroidism

Cases

Case 1

14 year boy, diagnosed with Duchenne Muscular Dystrophy at the age of 3.
Round face Plagiocephaly, Normal spine.
Normal hands and feet.
No cutaneous calcification.
Persistent Low Calcium, despite being treated with High dose calcium and Vitamin D Supplementation

Case 2

7 year girl presented with Childhood Obesity. Round face.
Significant brachydactyly of hands and feet. Lumbar lordosis.
Increased BMI affecting both central and peripheral parts of the body.
Weight(>99.6th), height(75th-91st).
No cutaneous calcification.

Case 3

12 years old boy presented in acute Hypocalcemic Tetany. History of pins and needles in hands and lips, recurrent spasm in hand and jaw for 7 month. Round face, Plagiocephaly and brachycephaly.
Evidence of shortening of the 4th and 5th metacarpals bilaterally.
No cutaneous calcification.

Discussion

- Type 1a is characterized by AHO and diminished Gs alpha activity.
- Half of the patients with PHP 1a have learning difficulties due to Gs alpha deficiency rather than chronic hypocalcaemia.
- Gs alpha deficiency in PHP1a may be associated with other hormone resistance (TSH/Gonadotropins).
- Genomic Imprinting: Inheritance of mutation from father is associated with PHP, where as inheritance of mutant gene from mother is associated with pseudo PHP.
- Patients with PHP type 1b present with hypocalcaemia and high PTH levels, however it is not associated with any clinical features of AHO.
- The locus responsible for PHP 1b has been found to reside on chromosome 20q13.3, the same region that contains the GNAS1 gene encoding Gs alpha.

Conclusions

- Phenotypic variability is common in PHP. It should be considered in the evaluation of persistent hypocalcaemia.
- Family history is important and needs to be carefully considered in the context of clinical presentation of hypocalcaemia.
- Complete biochemical evaluation is required in hypocalcaemia and hyperphosphatemia, especially in the absence of typical features of AHO.

Reference	Case1	Case2	Case3
Total Calcium (mmol/L)	1.80	2.02	1.50
Corrected Calcium (mmol/L)	1.70	1.97	1.44
Phosphate (mmol/L)	2.40	2.47	2.37
Alkaline Phosphatase (U/L)	150	200	333
Vitamin D mg/dl, (nmol/l)	10.9	37.8	<20
PTH (pmol/L)	20.1	29.9	27.8

Reference	Type 1a	Type 1b	Type 1c	Type 2	Pseudo-PHP
AHO	Yes	No	Yes	No	Yes
Ca+	Low	Low	Low	Low	Normal
PTH	High	High	High	High	Normal
Response to exogenous PTH	↓Ur cAMP & Phosphorus	↓Ur cAMP & Phosphorus	↓Ur cAMP & Phosphorus	Normal Ur cAMP, ↓Ur Phosphorus	Normal Ur cAMP & Phosphorus
GNAS gene mutations	Maternal inactivating mutation	Imprinting dysregulation	Few inactivating mutations	None	Paternal inactivating mutation
Hormone resistance	Multiple: PTH TSH,GHRH	PTH, TSH	Multiple: PTH, TSH, Gn	PTH only	None

AHO: Albrights Hereditary Osteodystrophy, cAMP: Cyclic Adenosine Monophosphate, TSH: Thyroid Stimulating Hormone, GN: Gonadotrophins, GHRH: Growth Hormone Releasing Hormone

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ESPE 2015 676--P3
Bone
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DOI: 10.3252/pso.eu.54espe.2015
Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology
PosterSessionOnline.com