PSEUDOHYPOPARATHYROIDISM (PHP): clinical heterogeneïty illustrated by 3 different cases.

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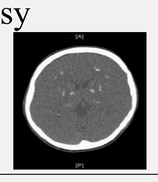
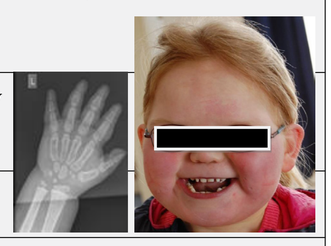
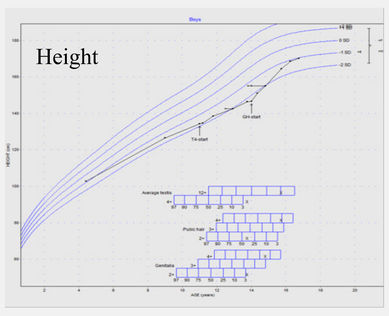
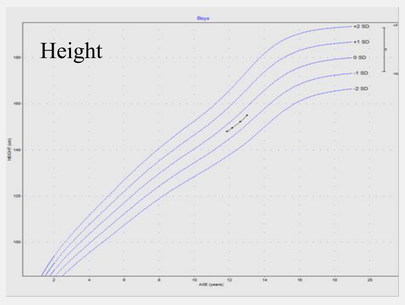
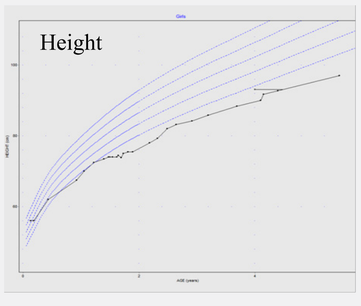
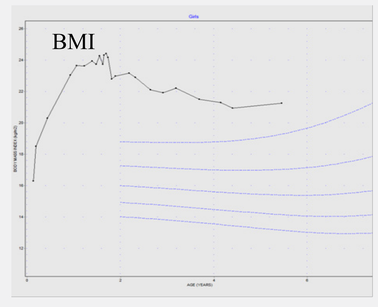
Pseudohypoparathyroidism represents a group of clinical and molecular heterogeneous disorders, characterized by functional hypoparathyroidism, caused by end-organ **resistance to the action of PTH**.
Pseudohypoparathyroidism manifests as **hypocalcemia, hyperphosphatemia** and **elevated plasma levels of PTH**.
A combination of features, also known as **Albright osteodystrophy** that includes disproportionate short stature, obesity, flattened face, brachydactyly and ectopic calcifications, may be present in PHP type 1A. However there are subgroups of PHP with normal phenotype.
We present 3 different cases:

Casus 1	Casus 2	Casus 3
13y old boy with fatigue and muscle cramps	11y old boy with therapy-resistant absence epilepsy Intracrebral calcifications on neuroimaging 	5y old girl with - severe neonatal hypoglycemia - congenital hypothyroidism - severe psychomotor retardation
Late onset growth failure (9y), Normal weight, Normal puberty	Normal height and weight Normal puberty	Early-onset growth failure (height -3.2 SD) Severe early-onset obesity (BMI + 2.6 SD)
No features of Albright osteodystrophy	No features of Albright osteodystrophy	Features of Albright osteodystrophy 
Mother is also affected	Identical twinbrother is not affected	No family members are affected
Hypocalcemia (6,7 mg/dl, ref: 8.9-10.1) Hyperphosphatemia (7,8 mg/dl, ref: 3.1-5.9) Elevated PTH (466 pg/ml, ref: 13-54) Associated multihormone resistance: - TSH resistance -> juvenile hypothyroidism - GHRH resistance –> GH deficiency	Hypocalcemia (6mg/dl, ref: 8.9-10.1) Hyperphosphatemia (9 mg/dl, ref: 3.1-5.9) Elevated PTH (349 ng/l, ref: 7-39) No associated hormone resistance	Hypocalcemia (2.12 mmol/l, ref: 2.23-2.53) Hyperphosphatemia (2.19 mmol/l, ref: 1-1.91) Elevated PTH (220 ng/l, ref 7-39) Associated multihormone resistance: - TSH resistance -> congenital hypothyroidism - GHRH resistance –> GH deficiency - Cortisol deficiency
Treatment with alfacalcidol, calcium supplements, levothyroxine, growth hormone	Treatment with alfacalcidol, calcium supplements	Treatment with alfacalcidol, calcium supplements, levothyroxine, cortisol
Catch-up growth and disappearance of fatigue and muscle cramps after initiation of treatment 	Disappearence of absence epilepsy after initiation of treatment 	Remaining poor growth, weight control, psychomotor retardation.  
Genetic testing revealed normal GNAS genes Genetic testing of DMR (differentially methylated region) of GNAS locus is awaiting	Genetic testing revealed normal GNAS genes No uniparental isodisomy Genetic testing of DMR (differentially methylated region) of GNAS locus is awaiting	Pathogenic mutation p.R231C in the GNAS1 gene

GNAS encodes **GS alpha**: this protein is required for normal transmembrane signal transduction by many hormones.
This gene is **imprinted in a tissue-specific manner**: the maternal allele is primarily expressed in renal proximal tubules
↔ both parentel alleles are expressed in bone.
Loss-of-function mutations in GNAS or epigenetic aberrations in DMR (differentially methylated region) of the GNAS locus
→ °failure of expression of GNAS in different tissues → °different types of PHP.

Pseudohypoparathyoridism type 1b, familial form	Pseudohypoparathyoridism type 1b, sporadic form	Pseudohypoarathyroidism type 1a
Heterzoygous deletions in maternal DMR of GNAS locus: STX16, NESP55, and/or A/B exons Loss of methylation in exon A/B	Paternal uniparental disomy in some Epigenetic aberrations in DMR	Heterozygous mutations in maternal GNAS gene that lead to haploinsufficiency of GS alfpha.
No Albright osteodystrophy PTH resistance in kidney, Partial resistance to TSH in some	No Albright osteodystrophy PTH resistance in kidney, Partial resistance to TSH in some	Albright osteodystrophy + early onset obesity PTH resistance in kidney Multihormone resistance

Substantial clinical and molecular overlap occurs between the different subtypes of PHP, what makes it challenging to diagnose this disease.

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