Variable phenotype and genetic findings in a cohort of patients with pseudohypoparathyroidism.

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Background
Pseudohypoparathyroidism is a group of rare disorders characterized by tissue insensitivity to multiple hormones (PTH, TSH, GHRG, LH, FSH) and Albright hereditary osteodystrophy (AHO) due to inactivating mutations or epigenetic defects of the GNAS.

Materials and methods
28 patients from 27 families with PHP

Hormone resistance
• PTH, Ca, P
• TSH, FT4
• IGF-1
• FSH/LH

AHO-features
• brachydactyly,
• short stature,
• obesity
• round face
• subcutaneous ossifications
• mental retardation

Molecular analysis
GNAS gene sequencing for patients with AHO-features

Complications
Cataract
Fahr’s syndrome
Nephrocalcinosis

Results

The reason for the first visit to a doctor
- Seizures 36%
- Obesity 25%
- PHP in sister 71.40%

Laboratory findings at the first evaluation

- Hypocalcemia+hypothyroidism n=19
- Hypocalcemia n=8
- Hypothyroidism n=1

Complications
- Fahr’s syndrome n=17
- Cataract n=5
- Without complications n=6

Hormone resistance

Genetic findings in patients with AHO-phenotype (n=13)
Sister and brother, mother – without any AHO-signs and HR
- Maternally inherited GNAS mutation
- De novo GNAS mutations
- No GNAS mutations

Conclusion
Obesity or hypothyroidism can precedes hypocalcaemia in PHP. Evaluation of serum Ca is important for all patients with seizures to avoid misdiagnosing. Absence of GNAS mutation in patients with AHO indicates overlap between PHPa and PHPb. Further investigations including MS-MLPA assay are planned to explore potential phenotype-genotype correlations in PTH.

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