CASE PRESENTATION-
PSEUDOHYPOPARATHYROIDISM

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Girl born in 2009

Born at the 38. week, resuscitation, 1 day of mechanical ventilation, CPAP, iv. atb.
  - 1 month: on the chest appeared a small, hard nodule, weeks later on the forehead

May of 2010, Szeged:
  - 1-2 cm big nodules all over the body- biopsy- osteoma cutis
  - Subclinical hypothyreosis- starts to take L-thyroxin (TSH: 14,0 mIU/L, fT4: 14,0 pmol/l)
  - Laboratory: Ca: 2,4 mmol/l, P: 2,03 mmol/l, PTH: 10,8 pmol/L, ALP: 274 U/L
  - Wrist X-ray: wider and shorter metacarpi

Albright’s herediter ostodystrophy (AHO)?
December of 2013, Debrecen
- Genetics consultation: AHO? sclerosis tuberosa? von Recklinghausen’s?
- Laboratory parameters: higher P, normal Ca, normal PTH, good TSH, fT4 with the hormone therapy
- 2014.03. head MRI: At the site of corpus pineale a 7x5x7 mm septated cyst (accidental finding)

February of 2015, Gyula, endocrinology
- Laboratory: higher P, normal Ca, normal PTH, good TSH, fT4 with the hormone therapy
- Deceber, 2015: higher P, normal Ca, increasing PTH
- February 2016: PTH: 304,6 pg/mL
- May 2016: Ca: 2.08 mmol/L, P: 1.92 mmol/L, PTH: 1037.00 pg/mL (norm: 10-65 pg/mL) -> sended to our Hospital for confirmation of the diagnosis
June, 2016: 2nd Dept. of Pediatrics:

Physical examination:

- Weight: 28.6 kg (pc: 90-97, SD: 2.6)
- Height: 117.1 cm (pc: 10-25, SD: 1.6)
- Face: round, slight hypertelorizm
- Short fingers, short IV. metacarpus
- Skin: cartilage-hard, slightly elevated lesions. Above the right eyebrow a 3 cm big, on the right side of the chest 5 cm big, chest, belly, back: multiple 0.5 cm big lesions
- Mentally normal, age-appropriate communication
Laboratory:
- Ca: 2.42 mmol/l, iCa 1.02 mmol/L, P: 1.73 mmol/l, PTH: 504 pg/mL (norm: 10-65 pg/mL), D3-vitamin 10.1 ng/mL
- Normal kidney function
- Neck US: thyroid gland hypoplasia

Wrist xray: bone-age 7 years and 6 months = biological age.
PARATHYROID HORMONE

Low concentration of calcium in blood

Release of parathyroid hormone

Efflux of calcium from bone

Decreased loss of calcium in urine

Enhanced absorption of calcium from intestine

Increased concentration of calcium in blood
Hypoparathyroidism:
- Low PTH, low Ca, high P levels
- Symptoms: paresthesia, tetany, cramps (Chvostek’s sign), abdominal pain, fatigue, headache, in severe case: seizures, heart arrythmy, bronchospasm

Hyperparathyroidism:
- High PTH, high Ca, low P levels
- Symptoms: kidney stones, weak bones, bone pain, depression
  - **Primary**: caused by higher production of PTH of the parathyroid gland
  - **Secondary**: caused by kidney disease, kidney failure, vitamin D deficiency (the kidney does not excrete the P, insoluble Ca-P forms and removes Ca from the circulation)
- **Pseudohypoparathyroidism** - the target organ (kidney) is insensible to PTH

- Ca level is low (the kidney does not reabsorb the Ca)
- PTH level is high (low Ca levels triggers the PTH excretion)
- P level high (coming from the bone together with Ca because of the PTH)
- Calcifications because of the insoluble Ca-P particles
- **Pseudohypoparathyroidism Ia** - next to the receptor of the PTH other hormone receptors are also dysfunctional (TSH, LH, FSH)

- **Pseudohypoparathyroidism Ib** - PTH receptor insensitivity

- **Albright’s hereditary osteodystrophy** - pseudohypoparathyreosis + typical phenotype

- **Pseudo-pseudohypoparathyroidism** - Albright’s phenotype without PTH resistency
Albright’s Phenotype

- Short statue
- Obesity
- Round face
- Brachydactily
- Short IV. metacarpus
- Subcutaneous ossifications
- Sexual infantilism
- (mental retardation)
**GENETICS - GNAS GENE**

- 20q13.2-13.3- Gsα
- Inheritance of the maternal or paternal allele mutation
- Maternal mutation: PHPT1a, paternal: PPHPT, both- PHPT1b (or imprinting error)
- Tissuespecific imprinting of the GNAS gene – in the kidney tubuli, thyroid gland, pituitary gland- only maternal genes are transcripted, the paternal are silenced by methylation.
- The symptoms appear after years – the paternal methylation appears later
### AHO-phenotype

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<tr>
<th>Hormonresistency</th>
<th>PHP1A: maternal GNAS1 (Gsα)</th>
<th>PHP1B: renal resistance, Imprinting error</th>
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<tr>
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<td>Tissue specific monoallelic expression</td>
<td>PHP1C: extremely rare, ~1a, not PTH</td>
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<tr>
<td>PHP1C: extremely rare, ~1a, not PTH</td>
<td>PHP1B: renal resistance, Imprinting error</td>
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<td>PPtPHP: paternal GNAS1 (Gsα)</td>
<td>Vitamin D deficiency</td>
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<td>CaSR activating mutation</td>
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In case of our patient the diagnosis of AHO was stated

For the genetical proving, blood was taken for verifying the GNAS gene mutation. 2nd Dept. Of Internal Medicine

Medicine taken: Euthyrox 50 ug, Vitamin D 2000 IU daily

**Therapeutical goal:** Normalisation of the serum calcium level by giving Vitamin D and Calcium (avoiding the hypercalcaemia – lowering the PTH level, kidney stones, cutaneous ossifications, avoiding osteopenia)
AHO – WHAT YOU HAVE TO KNOW

- Diagnosis suggested by dermatologist
- Hypothyroidism is observed early
- Laboratory:
  - First the PTH increases
  - Second: P level increases
  - The last: Ca level decreases (normocalcaemia is observed for a long time)
- Possibility for a molecular diagnosis (GNAS gene)
- Therapy: Vitamin D till the normalization of the Ca level and hormontherapy for hypothyroidism.