Premature adrenarche and pseudohypoparathyroidism – mechanistically linked or coincidence?

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European Reference Network for rare or low prevalence complex diseases
Network Bone Disorders (ERN BOND)

1. Background:

- Pseudohypoparathyroidism is a rare endocrine disorder characterized by resistance to the action of parathyroid hormone.
- Albright hereditary osteodystrophy (AHO) is the most common of 5 sub-types, presenting with a characteristic phenotype.

AIM: *To describe a case of premature adrenarche with pseudohypoparathyroidism, an as yet unreported combination.*

2. Case:

An otherwise well 8 year old girl presented to a Paediatric Endocrine Clinic with **early pubic hair development** suggestive of Premature Adrenarche.
Blood tests revealed:

- Hypocalcaemia
- Elevated phosphate
- Highly elevated PTH

a **biochemical diagnosis of pseudohypoparathyroidism**

She had **normal stature** (height 50th – 75th centile) and **no phenotypic features** of Albright Hereditary Osteodystrophy were identified on initial presentation (obesity, learning difficulties, brachydactyly, short stature, shortened 4th/5th metacarpals, dental hypoplasia or a rounded face).

Initial Blood Tests:

Analyte:	Value:	Units:	Ref. Range:
Calcium	1.59*	mmol/L	2.2-2.57
Adjusted Calcium	1.49*	mmol/L	2.2-2.57
Phosphate	2.78*	mmol/L	0.9-1.8
PTH	66.4*	pmol/L	1.6-6.9
Total 25-hydroxy chole calciferol	94	nmol/L	>50 (vit D adequate- no need for supplements)
TSH	4.8*	miu/L	0.27-4.2
Free T4	15.4	pmol/L	12-22

3. Treatment:

- Oral calcium carbonate
- Alfacalcidol

Corrected Calcium and phosphate levels normalised with treatment.

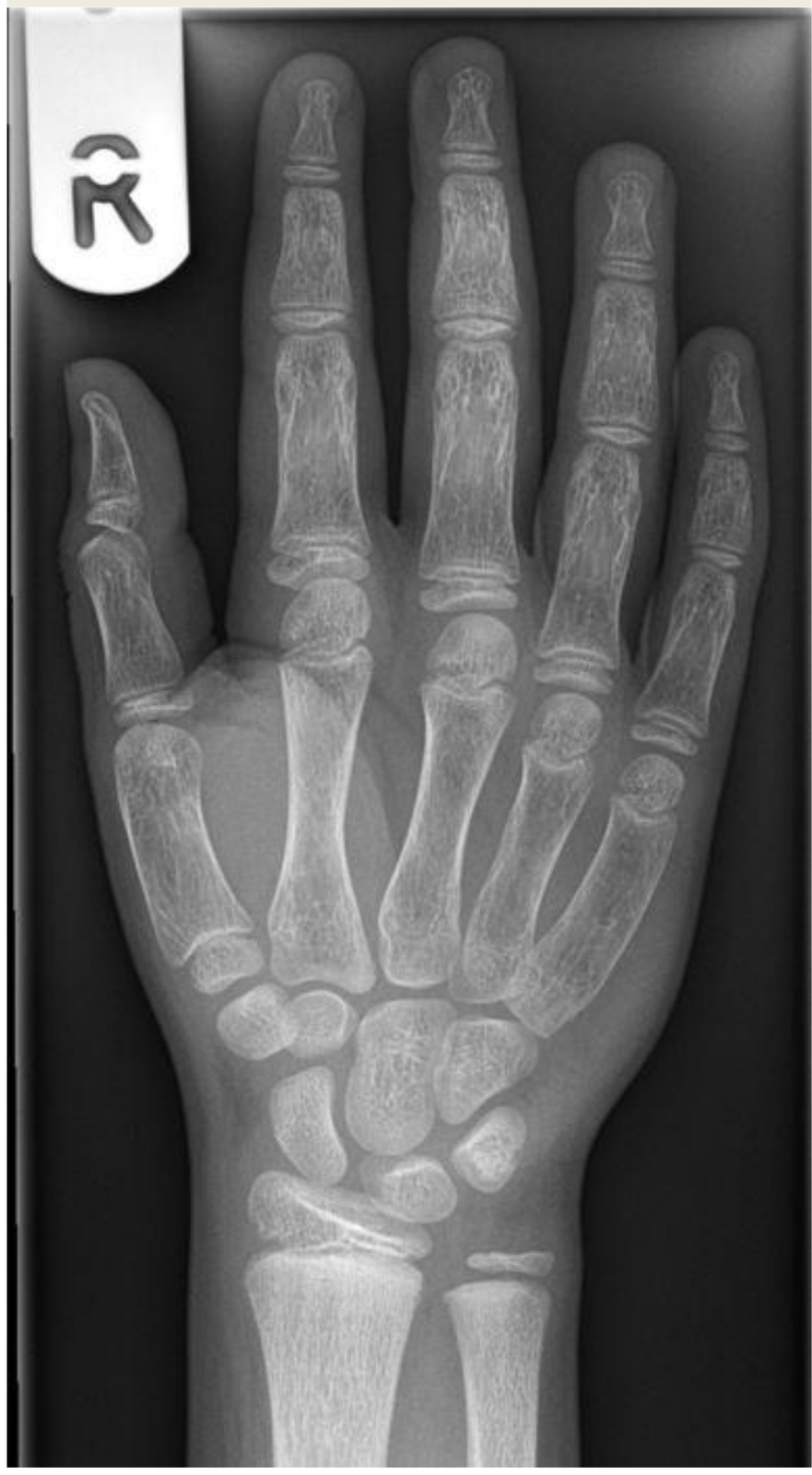

Image 1: Hand and wrist X-ray for bone age (non dominant)- "The fourth and fifth metacarpals appear shortened."

4. Outcome:

- Hand & Wrist for Bone Age (non dominant):

"The fourth and fifth metacarpals appear shortened" *-a phenotypical feature of AHO.*

- MRI head: No evidence of white matter calcification
- **Genetic testing:**
  - Microarray Comparative Genetic Hybridization - no abnormality seen
  - *Chromosone 20q13.32: GNAS exon A/B, GNASXL, NESPAS + NESP55 methylation – significant loss of mathernal methylation*
  - *No evidence of uniparental disomy*

5. Discussion:

- In our case the defect is likely due to an isolated imprinting error
- Recognition of a broader range of phenotypic features and underlying mutations has led to a novel classfication system of **iPPSD (inactivating PTH/PTHrP signalling disorders)**, developed by the EuroPHP network[1].
- GNAS1 mutations have been identified underlying various pseudohypoparathyroidism subtypes, resulting in reduced function of the G-protein coupled to the PTH receptor.
- G-proteins are also coupled to other hormone receptors; patients with AHO or iPPSD often present with other endocrine disorders, for example hypothyroidism.
- There are cases of individuals with GNAS1 mutations presenting concurrently with precocious puberty and pseudohypoparathyroidism[2] but no reported case of premature adrenarche and pseudohypoparathyroidism.

Glossary: PTH – parathyroid hormone; AHO – Albright Hereditary Osteodystrophy

6. Key Messages:

The underlying causes for PTH-related disorders are highly heterogenous with a variety of demonstrated underlying (epi)genetics; adrenarche is poorly understood; it is unclear if the premature adrenarche and pseudohypoparathyroidism in our case have a linked underlying mechanism.

References:

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