Obesity; A diagnostic dilemma

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Background

- Pseudohypoparathyroidism type 1a (PHP-1a) is a rare disorder caused by a maternally inherited mutation in the GNAS gene localized on chromosome 20 encoding for GS-α protein.
- PHP-1a is usually diagnosed in childhood due to a distinctive phenotype that includes:
  - Short stature
  - Round facies
  - Brachymetacarpia
  - Ectopic ossifications
  - Multi-hormone resistance
- These features are associated with resistance to parathyroid hormone (PTH).
- A more recently described feature of PHP-1a is early-onset obesity.
- The hypothalamic GS protein coupled melanocotin-4 receptor (MC4R) may mediate the central effects of leptin on inhibition of satiety.

Case

Presentation
- 3.4 yr ♂ Generalised tonic clonic seizure
- Hypocalcaemia

History
- Excessive weight gain since birth
- Birth- Term, BW 3.4 kg (25th centile), Solitary hypoglycaemic episode at birth
- 7 months [Weight 12.22kg (+3.01 SDS), Length 72.0cm (+0.72 SDS)]
- Dietetic support
- Prader-Willi and Beckwith ruled out
- Increasing BMI persisted
- 3.4 years [Weight 25.76kg (+4.34 SDS), BMI 25.71 kg/m2 (>99.6th centile)]
- Hypocalcaemic at time of seizure with Low Vitamin D and raised PTH.
- Skin calcinosis in mother

Examination
- Obese
- Round face
- Short digits
- Advanced bone age 4.6 years

Management and Progress
- Calcium and Vitamin D Supplementation
- Regular biochemical and weight monitoring
- Genetic analysis- confirmed diagnosis: ‘Albright’s hereditary osteodystrophy (AHO); pseudohypoparathyroidism (PHP type 1a)’

Investigations

Biochemistry

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<tr>
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<th>At Presentation</th>
<th>On Treatment - 6 months</th>
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<tbody>
<tr>
<td>Ca²⁺ mmol/L (2.20-2.70 mmol/L)</td>
<td>1.74</td>
<td>2.24</td>
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<tr>
<td>PO₄³⁻ mmol/L (0.9-1.8 mmol/L)</td>
<td>2.49</td>
<td>2.01</td>
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<tr>
<td>PTH pmol/L (1.3-9.3 pmol/L)</td>
<td>68.2</td>
<td>18.2</td>
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<td>Vit D nmol/L (70-200 nmol/L)</td>
<td>39</td>
<td>173</td>
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Radiology

Figure 2: X-ray left hand & wrist

Genetics

Heterozygous for an insertion of 8 nucleotides at cDNA position 388 (c.388_389insGGTTCATC) in the GNAS1 gene.

Learning Points

- Albrights should be considered in any child with a history of hyperphagia and early onset obesity
- Appropriate management ensures regulation of plasma calcium, bone mass and TSH resistance.
- Follow up should be comprehensive given the manifestations of the disease associated with being overweight.

References