The importance of urinary calcium measurement and genetic studies in differentiating Familial Hypocalciuric Hypercalcaemia (FHH) from Primary Hyperparathyroidism (PHPT)

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CASE HISTORY (Mother)
- A 56 year old lady with mild hypercalcaemia since 2004
- Diagnosed as Primary Hyperparathyroidism and had Parathyroidectomy in 2008 (Histology showed hyperplasia)
- No symptoms and no bony or renal complications
- Her vitamin D level was normal (on supplements)
- Ongoing mild hypercalcaemia post-surgery

CASE HISTORY (Son)
- A 21 year old man with mild hypercalcaemia since 2010
- PTH at the upper end of normal
- Diagnosed as Primary Hyperparathyroidism and planned to have Parathyroidectomy in March 2011
- No symptoms and no bony or renal complications
- His vitamin D level was normal (Not on supplements)

INVESTIGATIONS

Tests | Results | Normal values
---|---|---
Corrected Calcium | 2.76 mmol/L | 2.2 – 2.6
PTH level | 9.7 pmol/L | 1.6 – 6.9
Urinary calcium output | 3.96 mmol | 2.5 – 7.5
Ca/Cr clearance | 0.0142 | (>0.02 for PHPT)

Corrected Calcium levels

INVESTIGATIONS

Tests | Results | Normal values
---|---|---
Corrected Calcium | 2.76 mmol/L | 2.2 – 2.6
PTH level | 63.8 ng/L | 16 - 66
Urinary calcium output | <0.01 mmol | 2.5 – 7.5
Ca/Cr clearance | 0.0098 | (>0.02 for PHPT)

INVESTIGATIONS

Tests | Results | Normal values
---|---|---
Corrected Calcium | 2.76 mmol/L | 2.2 – 2.6
PTH level | 14.3 | 4.7 – 4.9
Urinary calcium output | 2.76 | 2.5 – 7.5
Ca/Cr clearance | 0.0142 | (>0.02 for PHPT)

FINAL DIAGNOSIS
- We advised to withhold parathyroid surgery for the son in view of his age, positive family history and very low urinary calcium excretion.
- Genetic analysis confirmed that both the mother and the son were heterozygous for c.61G>A (p.Gly21Arg) Calcium Sensing Receptor (CASR) variant.
- This gene has been reported in the literature to be associated with Familial Hypocalciuric Hypercalcaemia (FHH).
- The planned surgery for the son was later cancelled
- Both the mother and the son remained asymptomatic during their subsequent clinic follow up visits with continued mild biochemical derangements.

CONCLUSION AND LEARNING POINTS
- Familial Hypocalciuric Hypercalcaemia (FHH) is a benign condition, occurs as a result of inactivating mutation in the calcium sensing receptor (CASR) gene and is autosomal dominant.
- Inactivating mutation of the CASR affects the kidneys, enhancing calcium re-absorption and resulting in hypocalciuria
- Usually affects younger patients than patient with PHPT and usually with a positive family history
- Mild hypercalcaemia, normal or mildly raised PTH and very low Ca/Cr clearance ratio (typically <0.01) are typical features
- No renal or bone complications reported in literature
- Surgery is not indicated in an otherwise normal parathyroid glands, so it must be avoided.

REFERENCES
Christensen SE et al, Curr Opin Endocrinol Diabetes Obes. 2011 Dec;18(6):359-70
D A Heath, Reviews in Endocrine and Metabolic Disorders, 2000;1;291-296
A rare endocrine cause of severe resistant hypoglycaemia

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CASE HISTORY

- 68 year old lady
- Paroxysmal symptoms (sweating, palpitations, syncope and pre-syncope) for several weeks.
- History of significant weight loss.
- Chronic heavy smoker, but no alcohol intake
- Not on insulin or any other regular medications.

EXAMINATION

- Cachectic and had a non-tender palpable liver.
- No signs of decompensated chronic liver disease.
- Bedside capillary blood glucose reading was 0.9 mmol/L (NR 3.8-6.1).

INVESTIGATIONS

<table>
<thead>
<tr>
<th>Tests</th>
<th>Results</th>
<th>Normal values</th>
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<tbody>
<tr>
<td>ALP</td>
<td>383 iu/L</td>
<td>30 - 130</td>
</tr>
<tr>
<td>ALT</td>
<td>50 iu/L</td>
<td>0 - 50</td>
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<tr>
<td>GGT</td>
<td>635</td>
<td>0 - 76</td>
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<tr>
<td>Bilirubin</td>
<td>15 umol/L</td>
<td>&lt;21</td>
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<tr>
<td>AFP</td>
<td>&gt;1000 Mcg/L</td>
<td>&lt;5.8</td>
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<td>Glucose</td>
<td>1.2 mmol/L</td>
<td>4 - 7</td>
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<tr>
<td>Insulin</td>
<td>Undetectable</td>
<td></td>
</tr>
<tr>
<td>C-peptide</td>
<td>Undetectable</td>
<td></td>
</tr>
<tr>
<td>IGF-I</td>
<td>Undetectable</td>
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Image 1: CT abdomen showing multiple liver lesions

DIAGNOSIS

- Histology: high grade hepatocellular carcinoma
- Serum IGF-II concentration: 102 nmol/L (NR <10)
- IGF-II / IGF-I ratio >10

Non-Islet Cell Tumour Hypoglycaemia (NICTH) (Paraneoplastic hypoglycaemia)

POOR PROGNOSIS

- Patient continued to have hypos despite 10% IV-dextrose infusions and eating her normal 3 meals a day.
- Brief respite with IV-hydrocortisone
- Multiple hypoglycaemic seizures causing brain damage
- Deteriorated and deemed unfit for de-bulking surgery

IGF-II-INDUCED HYPOGLYCAEMIA PATHWAY

TUMOUR-INDUCED HYPOGLYCAEMIA

Parameter Islet Cell Tumours Non-Islet Cell Tumours

Glucose ↓ ↓
Insulin ↑ ↓
C-Peptide ↑ ↓
IGF-II/IGF-I ratio Normal Elevated (>10:1)

CONCLUSION AND LEARNING POINTS

- Non-Islet Cell Tumour Hypoglycaemia (NICTH) is a rare paraneoplastic phenomenon due to high IGF-II secretion by the tumour cells.
- Can be the presenting symptom of some advanced tumours, particularly tumours of epithelial and mesothelial origins
- Treating hypoglycaemia in such cases can be challenging as they tend to be severe and resistant to glucose replacement.
- Several other treatment options have been tried in literature (case reports only) such as glucocorticoids and somatostatin analogues, but nothing proven to be effective.

REFERENCES

Thipaporn et al. 2005
Marks & Teale 1998
Drake et al. 1998
Holt et al. 2003
Perros et al. 1996
Morbois-Trabut et al. 2004

Non-Islet Cell Tumour Hypoglycaemia (NICTH) (Paraneoplastic hypoglycaemia)