Idiopathic infantile hypercalcemia: presenting in childhood, diagnosed in adulthood – case report

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Introduction

- Hypercalcemia is known to be caused by a variety of pathologies or factors;
- Vitamin D plays a central role in calcium homeostasis, where a tight control of its metabolism is necessary;
- Inadequate 24-hydroxylase-enzyme (CYP24A1) activity leads to failure of 25-hydroxyvitamin and 1,25-dihydroxy-vitamin D3 inactivation, resulting in hypercalcemia.

Case report

An asymptomatic, 22-year-old woman was admitted in an Endocrinology appointment for evaluation of persisting hypercalcemia: 10.5-13.6 mg/dL (reference range: 8.6-10.2 mg/dL).

Medical history:
- The patient had suffered a transient period of polyuria in childhood (4-5-years-old) with calcium oxalate crystals in urine, diagnosed by her pediatrician as recurrent cystitis;
- Normal global development;
- Currently without any known disease or medication;
- No arterial hypertension;
- Born to nonconsanguineous parents; no other known familial cases.

Laboratory evaluation

<table>
<thead>
<tr>
<th>Parathyroid hormone</th>
<th>&lt;2.5 pg/mL (l)</th>
<th>7-65 pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-hydroxy-vitamin D3</td>
<td>22.4 ng/mL (insufficiency)</td>
<td>30-100 ng/mL</td>
</tr>
<tr>
<td>1,25-dihydroxy-vitamin D3</td>
<td>85 pg/mL (l)</td>
<td>18-78 pg/mL</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.6 mg/dL</td>
<td>0.5-1.1 mg/dL</td>
</tr>
<tr>
<td>Serum phosphorus</td>
<td>3.6 mg/dL</td>
<td>2.4-5.1 mg/dL</td>
</tr>
<tr>
<td>Angiotensin converting enzyme</td>
<td>25 U/L</td>
<td>8-52 U/L</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>324.9 ng/24 h (l)</td>
<td>100-320 ng/24 h</td>
</tr>
</tbody>
</table>

Renal ultrasound demonstrates medullary nephrocalcinosis

Imagologic evaluation

Genetic study and familial evaluation

- Sequence analysis of the CYP24A1 gene was performed, revealing that the patient has two mutations in heterozygosity:
  - c.1186C>T (p.Arg396Trp) and
  - c.1226T>C (p.Leu409Ser)

- Analytic and genetic study of first-degree relatives was mandatory (parents and 15-year-old sister):
  - Father: has the c.1186C>T (p.Arg396Trp) mutation in homozygosity, with normocalcemia, but decreased level of PTH (8.7 pg/mL); no signs of nephrocalcinosis.
  - Mother: is a carrier of the c.1226T>C (p.Leu409Ser) familial mutation, in heterozygosity; with normal analytic evaluation.
  - Sister: has two mutations in heterozygosity: c.1186C>T (p.Arg396Trp) and c.1226T>C (p.Leu409Ser). Analytic evaluation revealed hypercalcemia (10.5 mg/dL) and decreased parathyroid hormone (6.4 pg/mL); medullary nephrocalcinosis observed on renal ultrasound.

- A low-calcium diet, avoidance of vitamin D supplements and sun protection were recommended.

Conclusion

Idiopathic infantile hypercalcemia is an autosomal recessively inherited disease, with an unknown real prevalence. This particular case emphasizes two main issues:
1. The diagnosis of the underlying cause of hypercalcemia in Endocrinology turns out to be more complex, as the vitamin D has an important role, besides PTH.
2. The identification of patients with this disease as at-risk group brings a new aspect to the debate concerning vitamin D supplementation. More studies are necessary to understand the severity of this disease over time.

References / Bibliography