Brief report

Pseudohypoparathyroidism (Ia and Ib) and hypercalcitoninemia: a clinical long-term follow-up of two patients

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KEY WORDS: pseudohypoparathyroidism 1a, pseudohypoparathyroidism 1b, hypercalcitoninemia

Introduction

Pseudohypoparathyroidism (PHPT) is an unusual disease, which is characterized by the resistance of bones and kidney to PTH, followed by hypocalcaemia, hyperphosphataemia, glandular hypertrophy and hypersecretion of PTH. Patients with PHPT clinically manifest tetany seizures, soft tissue calcifications and many congenital malformations. Clinical symptoms may be different and depend on genetic defect or its selectivity with reference to the tissues.

At present we can distinguish three types of PHPT and pseudophyposparathyroidism. The disease usually appears in the infancy. Early diagnosis and vitamin D3 or calcium treatment seem to be the most important for patient’s condition. Too late treatment threatens with brain calcification followed by neurological defects and mental retardation.

In this paper we discuss two different patients (A.S., 32 years old male patient with PHPT type 1b, and L.M., 66 years old female patient with 1a PHPT) that during the treatment of hypocalcemia developed hypercalcitoninemia.

Subjects and methods

Our institutional ethics committee approved this study and written informed consent was obtained from the subjects. The clinical study was performed in accordance with the principles of the Helsinki Declaration.

Patients

A.S.
A 32-year-old Italian man was referred to “Azienda Ospedaliera Careggi” hospital (Florence) in 1986 because of recent complaint of severe asthenia, dating back at least 5-6 years, and paresthesias of the legs. His father was affected by Alzheimer disease since many years; he had five brothers which were in apparently good health. In the past, he had presented signs and symptoms of tetany during severe febrile episodes, characterized by muscle twitches, cramps and carpopedal spasms. He had no ever smoked. Moreover, he had arterial hypotension (105/80) with 70 b/min; his height was 173 cm, and his weight was 68 kg. There were no somatic phenotypic abnormalities but Chvostek and Trousseau signs (after 25-30 sec) at the first visit were clearly positive. Electromyography (EMG) and electroencephalogram (EEG) confirmed hypocalcemic signs. Intracranial calcifications of the basal ganglions were detected when computed tomography (CT) was performed.

Serum total calcium varied from 1.51 to 1.61 mmol/L, albumin 37-44 g/L, phosphate 1.51-1.66 mmol/L, and normal calcium 0.52-1.55 mmol/L. Serum intact PTH levels were 153 and 155 ng/L (normal range: 10-65), and 25(OH)D3 was 40 nmol/L (normal range: 25-100), serum 1-25(OH)D3 was 51.60 nmol/L (normal range: 30-144). Serum and urine magnesium and creatinine clearance were normal. Twenty-four-hour urine calcium was 28 mg. Bone formation and resorption markers were normal. Bone mineral densities measured by dual-energy X-ray absorptiometry (DEXA) were within normal limits at the lumbar spine. Intravenous infusion of 200 units of synthetic 1-34 PTH (Parathyrin®) over 10 minutes was associated with a failure to significantly rise urinary cyclic AMP (from 1.50 mmol/mg creatinine to 4.09 mmol/mg creatinine) and phosphate in urine (that increased only from 112.69 to 243.46 mmol/g creatinine) (Tab. I) in comparison with normal subjects and with hormonopenic hypoparathyroidism patients.

A series of standard provocative test were performed in this patient. TRH test (for TSH, GH and prolactin-PRL) (Tab. II), GNRH test (for LH, FSH, PRL) (Tab. III), AVP infusion test (for serum osmolality) (Tab. IV), glucagon test (for plasma glucose, insulin, serum Insulin C peptide, GH and cortisol) (Tab. V) were normal.

Basal serum calcitonin was in the normal range but after calcium and calcitriol supplementation significantly increased, during years 1986-2003 (Tab. VI). Thyroid ultrasound examination was always considered normal; no nodules were seen. Calcitonin values of relatives were in the normal range. Serum CEA was always in the normal range. Genetic analysis of GNAS1 gene showed an heterozygous T>C variant at the nucleotide position 493 (intron 5).

L.M.
A 66-year-old Italian lady was referred to “Azienda Ospedaliera Careggi” Hospital (Florence) in 1999 because of severe hypocalcemia (1.25 mmol/L) and marked increase of plasma PTH (772 ng/L) detected during an evaluation for unexplained seizures. Serum magnesium levels were in the normal range. CT scan detected intracranial severe basal ganglion calcifications. She was born in a very small town near Napoli (Southern Italy), but Chvostek and Trousseau signs (after 25-30 sec) at the first visit were clearly positive. Electromyography (EMG) and electroencephalogram (EEG) confirmed hypocalcemic signs. Intracranial calcifications of the basal ganglions were detected when computed tomography (CT) was performed.

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Table I - 1-34 PTH intravenous infusion test (200 UI) over 10 minutes. The peak response in normal subjects is 50- to 100-fold times basal; patient shows only a 2-fold increase.

<table>
<thead>
<tr>
<th></th>
<th>B1</th>
<th>B2</th>
<th>0-30 min</th>
<th>30-60 min</th>
<th>60-120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>P (ur)</td>
<td>104.29</td>
<td>112.69</td>
<td>243.46</td>
<td>238.95</td>
<td>129.16</td>
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<tr>
<td>Nephrogenous cAMP</td>
<td>1.84</td>
<td>1.5</td>
<td>2.34</td>
<td>2.61</td>
<td>4.09</td>
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Table II - TRH test (iv injection of 200 µg) (1987).

<table>
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<tr>
<th></th>
<th>Basal</th>
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<th>30' min</th>
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<th>120 min</th>
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<tr>
<td>GH (ng/mL)</td>
<td>1.2</td>
<td>0.5</td>
<td>0.4</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>TSH (mU/L)</td>
<td>4.64</td>
<td>26.69</td>
<td>26.31</td>
<td>18.40</td>
<td>9.72</td>
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<tr>
<td>PRL (mU/L)</td>
<td>2.5</td>
<td>8.2</td>
<td>8.0</td>
<td>4.1</td>
<td>12.1</td>
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Table III - GNRH test (iv injection of 100 µg) (1987).

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<th>30 min</th>
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<tr>
<td>FSH (mU/L)</td>
<td>5.0</td>
<td>5.6</td>
<td>5.9</td>
<td>6.8</td>
<td>5.5</td>
</tr>
<tr>
<td>LH (mU/L)</td>
<td>14.9</td>
<td>62.5</td>
<td>61.0</td>
<td>45.7</td>
<td>30.3</td>
</tr>
<tr>
<td>PRL (mU/L)</td>
<td>3.9</td>
<td>3.7</td>
<td>2.5</td>
<td>1.9</td>
<td>1.5</td>
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</table>

Table IV - AVP test (im injection of 4 mg).

<table>
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<th>15 h</th>
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<tr>
<td>Plasma osmolality (mOsm/L)</td>
<td>275</td>
<td>276</td>
<td>275</td>
<td>274</td>
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Table V - Glucagon test (iv injection of 500 µg) (1991).

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<th>90'</th>
<th>120'</th>
<th>150'</th>
<th>180'</th>
<th>210'</th>
<th>240'</th>
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<tbody>
<tr>
<td>Glucose (mg/dL)</td>
<td>77</td>
<td>131</td>
<td>83</td>
<td>71</td>
<td>60</td>
<td>71</td>
<td>79</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>5.3</td>
<td>57.9</td>
<td>10.6</td>
<td>5.5</td>
<td>4.0</td>
<td>3.6</td>
<td>4.0</td>
<td>4.5</td>
<td>4.1</td>
</tr>
<tr>
<td>C-peptide (pg/mL)</td>
<td>0.6</td>
<td>37.0</td>
<td>2.7</td>
<td>1.1</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>GH (ng/mL)</td>
<td>0.73</td>
<td>0.08</td>
<td>0.23</td>
<td>0.77</td>
<td>9.70</td>
<td>10.2</td>
<td>3.57</td>
<td>0.89</td>
<td>0.47</td>
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<tr>
<td>Cortisolo (nmol/L)</td>
<td>369.0</td>
<td>255</td>
<td>329</td>
<td>260</td>
<td>653</td>
<td>863</td>
<td>1012</td>
<td>982</td>
<td>815</td>
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Table VI - Calcitonin values during years of patient A.S.

<table>
<thead>
<tr>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mmol/L)</td>
<td>1.53</td>
<td>2.10</td>
<td>2.21</td>
<td>2.00</td>
<td>1.95</td>
<td>2.18</td>
</tr>
<tr>
<td>PTH (nmol/L)</td>
<td>18.3</td>
<td>14.5</td>
<td>21.6</td>
<td>22.1</td>
<td>14.6</td>
<td>18.2</td>
</tr>
<tr>
<td>Calcitonin (2-10 pg/mL)</td>
<td>11.3</td>
<td>10.5</td>
<td>8.99</td>
<td>16.7</td>
<td>51.9</td>
<td>15.4</td>
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</table>
Pseudohypoparathyroidism (Ia and Ib) and hypercalcitoninemia: a clinical long-term follow-up of two patients

Italy). She was the second of 8 relatives (5 sons, 3 daughters, Fig. 1); the relatives II-6 (male) and II-7 showed intracranial ganglion calcifications but they refused any other examination. Her menses were regular until the age of 52 years, but she had no pregnancy. She was operated on for bilateral eye cataract. Her heigth was 145 cm and her weight was 55 kg; she exhibit- ed also a round face, with minimal mental retardation. No signs of brachydactyly neither of heterotopic calcifications were present at the clinical and radiological examinations. From many years she suffered by diffuse unexplained paresthesias. Creatinine clearance, as well as 25(OH)D3 was 54,66 nmol/L (2.25-107.5); serum 1-25(OH)2D3 was 58,32 pmol/L (36-144) were normal. Bone mineral densities measured by dual-energy X-ray absorptiometry (DEXA) were lower than the normal limits at the lumbar spine (BMD: 0,758; T: –2,92). She manifested also a severe olfactory impairment, confirmed by olfactive evoked potentials test; no gustatory neither auditory abnormalities were found. Organ and non-organ specific antibodies were studied, but only anti-parietal cells of gastric mucosa antibodies were found positive; basal gastrin serum level was very high (356 pg/mL). Calcitonin serum basal levels were high (17,7 pg/mL). No other endocrine abnormality was found.

Hormone assays

All the hormonal determinations (fT3, fT4, TSH, Insulin, c-Peptide, LH, FSH, GH, prolactin, c-AMP, cortisol, PTH) were performed by standard laboratory methods (radioimmunometric or immunochemiluminometric or immunoenzymometric assays, as appropriate) in the Hormonal Section of the General Laboratory of Azienda Ospedaliera di Careggi and in the Nuclear Medicine Laboratory Unit of the University of Firenze. Serum calcitonin was evaluated by a two-site immunoradiometric assay using ELISA-hCT kit (CIS, Gil-sur-Yvette, France); normal basal levels were 2-10 pg/mL.

Genetic analysis of the GNAS1 gene

Genomic DNA was isolated from peripheral EDTA blood samples of the hypocalcemic and healthy population with the phenol/chloroform procedure. Exons 1-13 of the Gαs coding gene (GNAS1) were amplified in 50 mL by PCR reaction containing 67 mM Tris-HCl, 16.6 mM (NH4)2SO4, 5 mM MgCl2, 0.01% Tween-20, 200 µM each of the four deoxyribonucleotides, 0.4 mM of oligonucleotide primers and 1U of Polytaq (Polymed, Florence, Italy) (1). The length of the PCR products was analyzed on 3% agarose gels, stained with ethidium bromide and visualized with UV light. In each subject both strands of each exon were sequenced. Sequencing of the PCR products using both sense and antisense primers was performed using AmpliTaq BigDye Terminator kit and 3,100 Genetic Analyzer (Applied Biosystems).

Discussion

Pseudohypoparathyroidism is a rare disorder characterized by increased levels of PTH in spite of severe hypocalcemia and cised thyroid gland showed diffuse hyperplasia (not nodular) of C-cells in colloid goitre and immunohistochemistry examination detected positive reaction for calcitonin, cromogranin and CEA. During surgery no hypertrophic parathyroid glands were found. After the surgical intervention, patient was substituted with l-thyroxine (100 µg/die); calcitonin rapidly decreased to very low serum levels (Tab. VII). The diffuse paresthesias decreased in few days and at the end of the first month after surgery completely stopped; olfactory impairment remained. No mutation of GNAS1 gene were observed in this patient.

Table VII - Calcitonin values during years of patient L.M.

<table>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>1.25</td>
<td>2.08</td>
<td>2.28</td>
<td>2.37</td>
<td>2.26</td>
</tr>
<tr>
<td>PTH</td>
<td>772</td>
<td>526</td>
<td>430</td>
<td>240</td>
<td>291</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>17.7</td>
<td>29</td>
<td>54</td>
<td>82.3</td>
<td>2.2</td>
</tr>
</tbody>
</table>

* After total thyroideectomy.

Table VIII - Pentagastrin test (iv bolus injection of 0.1 µg/kg). CEA was 3,1 ng/mL, gastrin was 308 pg/mL (<108), calcium was 2,13 mmol/L.

<table>
<thead>
<tr>
<th></th>
<th>-15 min</th>
<th>0</th>
<th>1 min</th>
<th>2 min</th>
<th>3,5 min</th>
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<tr>
<td>Calcium</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PTH</td>
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<tr>
<td>Calcitonin</td>
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-15 min 64 69 160 192 151 148 128
hyperphosphatemia. Several forms of PHPT have been de-scribed: PHPT type 1a (typical Albright hereditary osteodo-
spy [AHO], absent response to PTH infusion, generalized hor-
mone resistance, reduced Gαα activity); pseudo-PHPT (typical
AHO, normal serum calcium levels); PHPT type 1b (normal
phenotype, defective response to PTH infusion, low serum cal-
cium, normal Gαα activity); PHPT type 1c (typical AHO, defec-
tive response to PTH infusion, generalized hormone resis-
tance, normal Gαα activity); PHPT type 2 (low serum calcium,
normal cAMP response to PTH infusion, defective urine phos-
phorus response to PTH infusion).

Very few data exist about C-cells dysfunction in patients with
PHPT; moreover, both normal calcitonin (CT) levels (2-4) and
increased CT levels (5-7) have been reported. Calcitonin is a
32 amino acid hormone secreted by thyroid C-cells; its receptor
is a member of the family of G protein-coupled receptors (8). Usu-
ally hypercalcitoninemia is due to medullary thyroid carci-
oma, and to several other conditions, such as hypergastrine-
mia, chronic lymphocytic thyroiditis and renal failure. The re-
cent prospective study of C-cell function in patients with PHPT
(9) seems to have demonstrated that, despite of calcitonin may
be found only in patients with PHPT 1a; it may be
associated to resistance to calcitonin, as suggested by the usual
impairment of G-protein transduction in patients with PHPT 1a (10)
and confirmed by the normal plasma calcitonin levels in patients
with PHPT 1b, in which resistance is typically restricted to
PTH only (11).

We studied two patients with PHPT, A.S. with type 1b and L.M.
with type 1a. In contrast with Vlaeminck-Guillem data (9) we
observed high calcitonin serum levels also in the patient with
PHPT 1a. No good explanation for the high calcitonin serum
level and secretion was found for the patient with PHPT 1b. We
were unable to demonstrate, during many years of follow-up,
any cause of hypercalcitoninemia to that patient, lymph-
phocytic chronic thyroiditis, hypergastrinemia, or medullary thy-
roid carcinoma were found. However, we have to consider that
patient’s calcitonin serum levels increased after calcium sup-
plementation. Calcium is one of the usual provocative stimulus
generally used worldwide to induce calcitonin response. The mecha-
nism underlying calcium-induced calcitonin release is not fully
understood and controversial (12). Calcium can operate direc-
tly on parafollicular or indirectly on gastrin-cells, inducing an increased re-
lease of gastrin and secondarily calcitonin increase. Calcium-
secreting receptor is expressed in human gastrinoma cells and
could be involved in the mechanism of calcium-evoked gastrin
release (13). So we may hypothesize that chronic calcium ad-
imistration is the mechanism by which our patient with PHPT
1b developed hypercalcitoninemia.

In the patient with PHPT 1a we observed high plasma levels of
calcitonin since the first examination. C-cells function in this
subject may be deranged by several different causes and mechanisms.
She had basal hypergastrinemia due to atrophic
peptic ulcer disease. Hypergastrinemia is one of the known
conditions able to induce hypercalcitoninemia (14). Moreover
chronic calcium administration to normalize serum calcium levels
could directly stimulate calcitonin serum levels. So, in this particular patient, three different mechanisms seems to take part in
hypercalcitoninemia: resistance to calcitonin, hypergastrine-
mia for atrophic gastritis, calcium administration. However C-
cells appear to respond adequately to the stimulating penta-
gastrin infusion inducing a marked rising in calcitonin, confirm-
ning the normality of C-cell function. An abnormal pentagastrin response is known to be a specific marker for medullary thyroid
carcinoma, but in our PHPT 1a patient pathological examination
failed to show any evidence of tumor in the excised gland, in agreement with the literature data (5, 15, 16), finding only C-
cell hyperplasia.

C-cell hyperplasia precedes the development of medullary thy-
roid carcinoma in multiple endocrine neoplasia type 2A
(MEN2A). Identification of abnormal calcitonin levels after a
prophylactic stimulus is a technique that has been widely used
to diagnose this preneoplastic condition in an early stage dur-
ing the development of medullary thyroid carcinoma, when total thyroidec-ency is likely to be curative. C-cell hyperplasia due to
some mechanism other than the presence of the PHPT gene
mutation may also happen in PHPT 1a kindreds. We cannot
exclude the likelihood of developing a medullary thyroid carci-
noma in our patient, for the several different mechanism con-
tributing to hypercalcitoninemia. At last the molecular basis of
the severe olfacotory abnormality, without any other abnormali-
ties regarding gustatory and auditory pathways, is obscure
considering the unique G proteins that regulate signal trans-
duction pathways related to vision, olfaction and taste (17-20).
In conclusion, hypercalcitoninemia may be mostly correlated
to calcium therapy in PHPT 1b subjects rather than the presence
of the genetic abnormality. On the contrary, hypercalcitonine-
ia seems to be a new described feature of patient with PHPT
1a, of which you to take in account when other different factors
for rising calcitonin levels are present, for the risk to develop
medullary tumors of the thyroid.

Acknowledgements

We acknowledge that the genetic evaluation was performed in
the Laboratory of the Regional Center for Heidelberg Endocrine
Tumors, directed by Prof. Maia Lulu Brandi.

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