Long-term complications of chronic hypoparathyroidism: a cross-sectional study

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Disclosures

• Attendance of European meeting on disease control in hypoparathyroid patients (2017/2018) – Shire

• Grant: FWO Vlaanderen (1196520N)
Introduction

Hypocalcemia
Hyperphosphatemia
Hypoparathyroidism
Pseudohypoparathyroidism

Figure 1. Control of Mineral Metabolism by Parathyroid Hormone.

1 Shoback, NEJM 2008.
Introduction

• Rare disease – prevalence:
  – Denmark: 26/100.000 \(^{(2,3,4)}\)
  – Scotland: 40/100.000 \(^{(5)}\)
  – USA: 37/100.000 \(^{(6)}\)

Introduction

• Etiology:
  – Postsurgical
  – Nonsurgical
  – Pseudohypoparathyroidism
Introduction

• Etiology:
  – Postsurgical \(^7\)
    • Most frequent form > 75%
    • Thyroid surgery
      – Often transient hypocalcemia
      – 7% permanent/chronic
      – Gender difference $\text{♀} > \text{♂}$

\(^7\) Shoback et al, Clin Endocrinol and Metab 2016.
Introduction

• Etiology:
  – Nonsurgical\(^{(8,9)}\)
    • Autoimmune: isolated – APS1
    • Magnesium deficiency
    • Genetic: DiGeorge, CHARGE, HDR…
    • Post-radiation
    • Infiltrative: sarcoïdosis, amyloïdosis, metastases
    • Wilson’s disease, hemochromatosis
    • Idiopathic

\(^{8}\) Siraj et al, Endocrinol Metab Clin North Am 2018. \(^{9}\) Gafni et al, NEJM 2019
<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Locus</th>
<th>Gene</th>
<th>OMIM</th>
<th>Associated Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>22q11.21-q11.23</td>
<td>TBX1</td>
<td>184800</td>
<td>Thymic hypoplasia w/ immune deficiency, conotruncal cardiac defects, cleft palate, dysmorphic facies, short stature, gastrointestinal issues, thrombocytopenia, cognitive delay, psychiatric disorders. Pathogenetic variants in TBX1 may also cause isolated hypoparathyroidism.</td>
</tr>
<tr>
<td></td>
<td>10p14</td>
<td>SELEN</td>
<td>603162</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>8q12.2 7q11.11</td>
<td>CHID7</td>
<td>214800</td>
<td>Coloboma, heart defects, chondal atresia, poor growth, genital hypoplasia, ear anomalies/deafness</td>
</tr>
<tr>
<td></td>
<td>10p14</td>
<td>GATA3</td>
<td>146255</td>
<td>Deafness, renal dysplasia</td>
</tr>
<tr>
<td>AR or AD</td>
<td>1q42.3</td>
<td>TBCE</td>
<td>241410</td>
<td>Growth retardation, developmental delay, microcephaly, microphthalmia, small hands/feet Medullary stenosis, tiet abnormalities</td>
</tr>
<tr>
<td></td>
<td>11q12</td>
<td>FAM11A</td>
<td>127000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mtDNA</td>
<td>MTIF</td>
<td>530000</td>
<td>Ectopia, eye disease, heart block</td>
</tr>
<tr>
<td></td>
<td>mtDNA</td>
<td>MTP</td>
<td>557000</td>
<td>Anemia, panencephaly dysfunction</td>
</tr>
<tr>
<td></td>
<td>mtDNA</td>
<td>MTP</td>
<td>540000</td>
<td>Myopathy, oculopathy, acidosis, stroke</td>
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<tr>
<td></td>
<td>2p23</td>
<td>ECHN</td>
<td>609016</td>
<td>Hypoglycemia, hypotonia</td>
</tr>
<tr>
<td>AR or AD</td>
<td>6p24.2</td>
<td>GCM2</td>
<td>603716</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Xq26-27</td>
<td>SOX3</td>
<td>307000</td>
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</tbody>
</table>

**Disorder of Parathyroid Gland Secretion**

- **Neonatal hypoparathyroidism due to maternal hypercalcemia**

  Causes early neonatal hypocalcemia; transient

- **Hypomagnesemia**

  Multiple genetic and acquired causes; inhibits PTH secretion and PTH sensitivity

- **Hypoparathyroidism**

  Inhibits PTH secretion via activation of the CaSR

- **PTH gene mutations**

  AR or AD

  11p15.3

  PTH

  168450

- **Autosomal Dominant Hypocalcemia (activating)**

  Type 1

  3q13.3-21

  CaSR

  601198

  Type 2

  19p13.3

  GNAS

  615361

- **Variable degree of severity, hypomagnesemia, hypercalcina |

**Parathyroid Gland Damage/Destruction**

- **Complication of Neck Surgery**

  May be transient

- **Infiltrative diseases/heavy metals**

  Hemochromatosis, Wilson disease, metastases

- **Autoimmune Hypoparathyroidism**

  Unknown

  Maybe associated with other autoimmune diseases; possibly HLA-associated

- **Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome** (APECED)

  AR

  21q22.3

  AIRE

  240300

VCFS = velocardiofacial syndrome; AD = autosomal dominant; AR = autosomal recessive; XR = X-linked recessive; CHARGE = Coloboma, Heart defects, chondal Atresia, Retarded growth, Genital hypoplasia, Ear anomalies/deafness; PTH = parathyroid hormone; CaSR = calcium-sensing receptor; mt = mitochondrial; MELAS = Mitochondrial Encephalopathy, Lactic acidosis, and Stroke-like episodes syndrome; LCHAD = Long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency.

9 Gafni et al, NEJM 2019
Introduction

- Etiology:
  - Pseudohypoparathyroidism \(^{(10,11)}\)

### Table 1. Clinical, Biochemical, and Genetic Features of Pseudohypoparathyroidism and Related Disorders

<table>
<thead>
<tr>
<th></th>
<th>PHP1a</th>
<th>PHP</th>
<th>PHP1b</th>
<th>PHP1c</th>
<th>PHP2</th>
<th>POH</th>
<th>OC</th>
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<tbody>
<tr>
<td>AHO manifestations</td>
<td>Yes</td>
<td>Yes</td>
<td>No*</td>
<td>Yes</td>
<td>No</td>
<td>No*</td>
<td>No</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>↓</td>
<td>N</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Serum phosphate</td>
<td>↑</td>
<td>N</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Serum PTH</td>
<td>↑</td>
<td>N</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Other hormonal resistance</td>
<td>Yes (superficial)</td>
<td>No (superficial)</td>
<td>No*</td>
<td>Yes (superficial)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Heterotopic ossification</td>
<td>Yes (superficial)</td>
<td>Yes (superficial)</td>
<td>No</td>
<td>Yes (superficial)</td>
<td>No</td>
<td>Yes (deep tissues)</td>
<td>Yes (superficial)</td>
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<tr>
<td>Response to PTH:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>urinary cAMP</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>urinary phosphate</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td>↑</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>In vitro Gs-alpha activity</td>
<td>↓</td>
<td>AD</td>
<td>N</td>
<td>AD or Sporadic</td>
<td>Sporadic</td>
<td>AD or Sporadic</td>
<td>AD or Sporadic</td>
</tr>
<tr>
<td>Inheritance</td>
<td>AD</td>
<td>AD</td>
<td>AD or Sporadic</td>
<td>AD</td>
<td>Maternal inactivating mutations</td>
<td>Maternal inactivating mutations (rare)</td>
<td>AD or Sporadic</td>
</tr>
<tr>
<td>GNAS defect</td>
<td>Maternal inactivating mutations</td>
<td>Paternal inactivating mutations</td>
<td>AD</td>
<td>AD or Sporadic</td>
<td>None</td>
<td>Paternal inactivating mutations</td>
<td>AD or Sporadic</td>
</tr>
</tbody>
</table>

*Except for some cases.

PHP, pseudohypoparathyroidism; PHP, pseudopseudohypoparathyroidism; POH, progressive osseous heteroplasia; OC, osteoma cutis; AHO, Albright’s hereditary osteodystro- phy; PTH, parathyroid hormone; cAMP, cyclic adenosine monophosphate; GNAS, guanine nucleotide-binding protein, alpha-stimulating activity polypeptide; ↓, decreased; ↑, increased; N, normal; AD, autosomal dominant.

\(^{10}\) Lemos et al, Hum Mutat 2015, \(^{11}\) Mantovani et al, Nat Rev Endocrinol 2018.
Introduction

• Etiology:
  – Pseudohypoparathyroidism
  • AHO (Albright Hereditary osteodystrophy)
Introduction

- Symptoms: hypocalcemia (7,9)
  - Paresthesia, cramps, tetany
  - Seizures
  - Arrhythmias

- Reduced quality of life (12-14)
Introduction

• Conventional therapy \(^{(1)}\)
  – (active) vitamin D
  – calcium supplements

• rhPTH (1-84) \(^{(15)}\)
  – Reduction dose conventional therapy \(^{(16,17)}\)
  – Improved QoL \(^{(18)}\)

Introduction

• Complications (7,19)
  – Renal
  – Cerebral
  – Bone
  – Cardiovascular
  – Cataract
  – ...

• Increased mortality (20,21)

Long-term complications in patients with chronic hypoparathyroidism: a cross-sectional study

K David, C Moyson, D Vanderschueren and B Decallonne

Department of Endocrinology, University Hospitals, Leuven, Belgium
Objectives

- Characterize cohort of hypoparathyroid patients
- Determine renal and cerebral complications
- Compare current standard of care with 2015 guideline

European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults

Jens Bollerslev1,2,*, Lars Rejnmark3,*, Claudio Marcoce4, Dolores M Shoback5, Antonio Sittges-Serra4, Wim van Biesen7 and Olaf M Dekkers8,9,10

23 Bollerslev et al, European journal of Endocrinology 2015
Study design

- Retrospective cross-sectional

Unique patients based on electronic keyword query (n = 319)

No hypoparathyroidism or pseudohypoparathyroidism (n = 83)

Hypoparathyroidism (HP) (n = 225)

Pseudohypoparathyroidism (PHP) (n = 11)

Hypoparathyroidism < 1 year (n = 52)

Hypoparathyroidism ≥ 1 year (n = 173)

< 1 year follow-up (n = 14)

≥ 1 year follow-up (n = 159)

Post-surgical hypoparathyroidism (PSHP) (n = 143)

Non-surgical hypoparathyroidism (NSHP) (n = 16)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 170</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>39.4 (67)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.11 ± 15.65</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>16.58 ± 14.65</td>
</tr>
<tr>
<td>Aetiology</td>
<td></td>
</tr>
<tr>
<td>Post-surgical hypoparathyroidism</td>
<td>84.1 (143)</td>
</tr>
<tr>
<td>Total thyroidectomy</td>
<td>65.0 (93)</td>
</tr>
<tr>
<td>Total thyroidectomy + neck dissection</td>
<td>13.3 (19)</td>
</tr>
<tr>
<td>Hemithyroidectomy</td>
<td>8.4 (12)</td>
</tr>
<tr>
<td>Parathyroidectomy (partial/total)</td>
<td>7.7 (11)</td>
</tr>
<tr>
<td>Other types of neck surgery</td>
<td>5.6 (8)</td>
</tr>
<tr>
<td>Non-surgical hypoparathyroidism</td>
<td>9.4 (16)</td>
</tr>
<tr>
<td>Pseudo-hypoparathyroidism</td>
<td>6.5 (11)</td>
</tr>
<tr>
<td>Medical treatment</td>
<td></td>
</tr>
<tr>
<td>Alfacalcidol</td>
<td>95.9 (163)</td>
</tr>
<tr>
<td>Mean dose (µg)</td>
<td>1.31 ± 0.74</td>
</tr>
<tr>
<td>Vitamin D₃ (± calcium supplement)</td>
<td>35.3 (60)</td>
</tr>
<tr>
<td>Mean dose (IU)</td>
<td>1067 ± 692</td>
</tr>
<tr>
<td>Calcium supplement (± vitamin D₃)</td>
<td>78.2 (133)</td>
</tr>
<tr>
<td>Mean dose (mg)</td>
<td>1035 ± 507</td>
</tr>
<tr>
<td>Vitamin D₃ + calcium supplement</td>
<td>31.8 (35)</td>
</tr>
<tr>
<td>Anticalciuretic</td>
<td>14.1 (24)</td>
</tr>
</tbody>
</table>

*Table 1* Patient characteristics of total cohort. Data are presented as mean ± s.d. or % (n) for quantitative and categorical data respectively.
### Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>n = 170</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraesthesia and/or cramps</td>
<td>15.9 (27)</td>
</tr>
<tr>
<td>Urinary calcium excretion</td>
<td>75.9 (129)</td>
</tr>
<tr>
<td>Mean renal calcium excretion (mmol/24 h)</td>
<td>6.20 ± 3.79</td>
</tr>
<tr>
<td>Exceeding upper limit</td>
<td>36.4 (47)</td>
</tr>
<tr>
<td>History of seizures</td>
<td>8.8 (15)</td>
</tr>
<tr>
<td>History of kidney stones</td>
<td>14.7 (25)</td>
</tr>
<tr>
<td>Hospitalization due to hypocalcaemia</td>
<td>4.7 (8)</td>
</tr>
<tr>
<td>Renal imaging</td>
<td>51.2 (87)</td>
</tr>
<tr>
<td>Nephrocalcinosis and/or stones</td>
<td>21.8 (19)</td>
</tr>
<tr>
<td>Cerebral imaging</td>
<td>25.9 (44)</td>
</tr>
<tr>
<td>Intracerebral calcifications</td>
<td>25.0 (11)</td>
</tr>
</tbody>
</table>

**Table 2** Complications in the total cohort. Data are presented as mean ± s.d. or % (n) for quantitative and categorical data, respectively.
History of kidney stones and seizures according to disease etiology

- Postsurgical (n=143):
  - Kidney stones: 15.4%
  - Seizures: 4.2%

- Nonsurgical (n=16):
  - Kidney stones: 12.5%
  - Seizures: 25%

- PseudoHP (n=11):
  - Kidney stones: 9.1%
  - Seizures: 45.5%

Statistical significance:
- Kidney stones vs. Nonsurgical: $p < 0.001$
- Seizures vs. PseudoHP: $p < 0.01$
Imaging: renal and cerebral calcifications according to disease etiology

- Postsurgical (n=68/31): 27.9% Renal calcifications, 6.5% Cerebral calcifications
- Nonsurgical (n=12/8): 6.3% Renal calcifications, 14.3% Cerebral calcifications
- PseudoHP (n=7/5): 60% Cerebral calcifications

Statistical significance:
- Renal calcifications: p < 0.001
- Cerebral calcifications: p < 0.05
Complications: renal

- Increased risk for renal insufficiency
  - Both PSHP and NSHP \(^{2,3,21}\)

- Increased risk for kidney stones
  - PSHP \(^2\)

- Increased risk for nephrocalcinosis
  - Both PSHP and NSHP \(^{24}\)

\(^2\) Underbjerg et al, JBMR 2013. \(^3\) Underbjerg et al, JBMR 2015, \(^{21}\) Vadiveloo et al, Clinical Endocrinology 2018, \(^{24}\) Mitchell et al, JCEM 2012, Images: Case courtesy of Dr Jeremy Jones, Radiopaedia.org, rID: 6211 / Case courtesy of Dr Laughlin Dawes, Radiopaedia.org, rID: 36024
Complications: renal

- Management guidelines (9, 23, 24)
  - Kidney function
    - Every 3 to 6 months
  - 24h urine collection
    - Every 6 to 12 months
  - Imaging
    - Clinically indicated vs. every 1 to 5 years

Complications: cerebral

- High prevalence of cerebral calcifications
  - 50\% (25)
- Increased risk for seizures
  - Both PSHP and NSHP (3,21,26)
- Increased risk for neuropsychiatric symptoms
  - Both PSHP and NSHP (3,26)
- Relationship with calcifications?

Complications: cerebral

- Management guidelines (9, 23, 24)
  - Imaging?
    - As clinically indicated?

Complications: cardiovascular

- Increased cardiovascular disease
  - NSHP (3,21)

- Increased risk ischemic heart disease
  - NSHP (3)

- Management guidelines (9,23,24)
  - ???

Complications: bone

• Decreased bone turnover – higher bone mineral density (27)

• Fracture risk?
  – Increased risk fracture upper extremity in NSHP (3)
  – Increased risk vertebral fractures in idiopathic hyporathyroidism (28)
  – No increased fracture risk (21)

• PHP lower bone mineral density than NSHP (29)

\(^3\) Underbjerg et al, JBMR 2015, \(^{21}\) Vadiveloo et al, Clinical Endocrinology 2018, \(^{27}\) Rubin et al, JBMR 2008, \(^{28}\) Chawla et al, JCEM 2017, \(^{29}\) Underbjerg et al, JBMR 2018
Complications: bone

- Management guidelines \(^{(9,23,24)}\)
  - DXA scan:
    - As clinically indicated \(^{(23,24)}\)
    - Advise against routine DXA scan \(^{(9)}\)

Complications: cataract

- Increased risk
  - NSHP \(^3\)

- Management guidelines
  - Ophthalmological exam
    - As clinically indicated \(^{24}\)
    - Regularly \(^9\)

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Remaining challenges

• Hypoparathyroidism during pregnancy (30)
  – Case series
  – Calcium and (active) vitamin D treatment is safe
  – $1,25(\text{OH})_2\text{D}_3$ increases 2 to 3 fold during pregnancy
  – Close monitoring is necessary

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(30) Khan et al, Eur J Endocrinol 2019
Remaining challenges

• Hypoparathyroidism after Roux-en-Y Gastric Bypass
  – Increased risk hypocalcemia after thyroidectomy \(^{(31)}\)
  – Often challenging – reduced calcium uptake \(^{(32,33)}\)
  – Calcium citrate
  – Revision of RYGB

Remaining challenges

• Optimalization of the diet
  – Calcium-rich
  – Low in sodium

• Optimalization of conventional treatment
  – Non active vitamin D supplements
  – Calcium citrate vs. carbonate
  – Magnesium status
  – Increased attention other interfering drugs (PPI, antiresorptives, diuretics...)

Remaining challenges

• New treatments
  – rhPTH (1-84) (15)
  – Pharmacological studies with long acting PTH analogues (34) and PTHrP analogues (35)
  – ? CaSR antagonists in activating CaSR mutation in mice (36)
  – ? Allotransplantation (37, 38)

• Reduce morbidity and mortality?
Thank you for your attention

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References

References


Images: Biorender (www.biorender.com)