

## Primary hyperparathyroidism – sporadic and hereditary forms – etiology and pathogenesis

Peter Vestergaard, Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark

Peter Schwarz, Research Center of Ageing and Osteoporosis, Department of Medicine and Faculty of Health Science, Glostrup Hospital and Copenhagen University, Denmark

Bo Abrahamsen, Department of Endocrinology section F, Glostrup Hospital and Clinical Institute, University of Southern Denmark, Denmark

Kim Brixen, Department of Endocrinology M and Clinical Institute, University of Southern Denmark and Odense University Hospital, Denmark

### Correspondence:

Peter Vestergaard MD PhD DrMedSc  
The Osteoporosis Clinic  
Department of Endocrinology and Intern Medicine (MEA)  
Aarhus University Hospital  
Tage Hansens Gade 2  
DK-8000 Aarhus C  
Denmark  
Telephone + 45 89 49 76 52  
Fax + 45 89 49 76 84  
E-mail [p-vest@post4.tele.dk](mailto:p-vest@post4.tele.dk)

## 1. Background:

In most cases of primary hyperparathyroidism (PHPT) etiology is unknown. Parathyroid cells may grow from a single clone of cells, which may form an adenoma. In case of an adenoma the clone grows in a sigmoid pattern, i.e. after an initial phase of slow growth, a rapid growth phase ensues and finally a plateau is reached (fig. 1a). Little is known about the causes of single adenomas, however, many parathyroid adenomas harbor somatic mutations and rare cases are due to germline mutations [1]. More is known on the causes of hyperplasia, where all parathyroid glands are affected. In hyperplasia the growth pattern is usually exponential (fig. 1b). Hyperplasia may be caused by germ-line mutations, exposure to lithium, hyper-phosphatemia (e.g. in chronic renal disease) or long-standing hypovitaminosis D.

## 2. Etiology:

### 2.1 Mutations:

#### 2.1.1 Somatic mutations

Somatic mutations in the adenoma tissue have been reported in a varying proportion of patients with PHPT [1]. As many as 20-40% of sporadic parathyroid adenomas may contain somatic mutations in the Cyclin-D1/PRAD1 gene, which is in control of cell division, and thereby may lead to formation of clones of cells resulting in adenomas. Also, somatic mutations in the BRCA and retinoblastoma gene have been reported in parathyroid adenomas [2].

#### 2.1.2 Germline mutations

These mutations are present in all cells but only expressed in the parathyroid cells and *e.g.* the parafollicular C-cells (in multiple endocrine neoplasia (MEN) type 2) or pituitary cells (in MEN type 1) [3].

The mutations are seen in genes controlling cell division (HRPT1/CDC73), tumor suppressor genes (multiple endocrine neoplasia type 1, MEN1) or a gain of function as in MEN2. Some hereditary conditions have only been associated with PHPT on a case basis. All in all hereditary conditions represent less than 10% of all cases of PHPT.

##### 2.1.2.1 Mutations in the MENIN gene

The MENIN gene (OMIM 131100) is a tumor suppressor gene localized on chromosome 11. Usually MENIN inhibits the transcription factor JunD [4]. The mutations prevent MENIN from binding to JunD, which leads to neoplasia from lack of growth control [5].

MENIN gene mutations may lead to multiple endocrine neoplasia with varying combinations of PHPT, pituitary tumors, and neuro-endocrine tumors (gastrinomas, VIPomas, glucagonomas, insulinomas, carcinoid tumors etc.) [3]. However, some MENIN gene mutations may be associated with isolated familial PHPT [6]. The mutations are rather varied, and often only a few families have been described with each mutation [7-9].

The phenotype is that of PHPT, although screening may detect the patients in an earlier age than seen in sporadic cases.

PHPT is one of the most frequent manifestations of MENIN gene mutations, up to 86% of patients being affected [10]. Usually all four parathyroid glands are affected by hyperplasia [3]. Moreover, ectopic parathyroid glands may be localized in the thymus, which may be considered in surgical management as the disease tends to be more aggressive and have a higher recurrence rate than for other mutation types [11].

##### 2.1.2.2 Mutations in the RET proto-oncogene

RET (OMIM 164761) is short for re-arranged during transfection. Mutations in RET are “gain-of-function” mutations, *i.e.* result in increased proliferation. RET mutations may be associated with a) familial medullary thyroid carcinoma only (FMTC only), b) multiple endocrine neoplasia type 2A

(OMIM 171400) with medullary thyroid carcinoma (close to 100% of MEN2a-patients), pheochromocytoma (50% of patients), and PHPT (25% of patients) and c) multiple endocrine neoplasia type 2B (OMIM 162300) medullary thyroid carcinoma, pheochromocytoma, and a Marfanoid habitus, but rarely PHPT [3]. A genotype-phenotype correlation exists [12]. Thus mutations in codon 634 are the prototype of mutations in the RET proto-oncogene associated with primary hyperparathyroidism [13]. However, also other codons such as 609, 611, 618, 620, 630, 633, 649, 768, 790, 791, 804, and 891 may be associated with PHPT [13]. In contrast to MENIN gene mutations, patients with RET proto-oncogene mutations may present with only one adenoma [13].

### **2.1.2.3 Mutations in the HRPT2 gene (Parafibromin, CDC73 gene)**

These mutations (OMIM 607393) may be associated with familial hyperparathyroidism [14-16] or hyperparathyroidism-Jaw Tumor (HPT-JT) syndrome [17-19]. In contrast to the other inherited syndromes of hyperparathyroidism, these mutations often are associated with parathyroid cancer [14]. Little seems to separate patients harboring HRPT2 mutations presenting with isolated familial PHPT from those with parathyroid cancer [14].

The HPT-JT is a syndrome of PHPT or parathyroid cancer associated with ossifying jaw tumors, and other associated tumors such as hamartomas of the kidneys [18]. A large proportion of patients have recurrence of parathyroid neoplasia after removal of one affected parathyroid gland (17.6% after 13.7 years [18] and 80% after 30 years [20]).

### **2.1.2.4 Homozygous mutations in the calcium sensing receptor (CaSR)**

Heterozygous inactivating mutations in the CaSR (OMIM 601199) lead to familial (benign) hypocalciuric hypercalcaemia (FHH) – OMIM 145980 [5]. This is a condition with hypercalcaemia brought about by increased calcium reabsorption in the kidneys leading to a low calcium excretion in the urine [21]. Homozygous CaSR mutations leads to neonatal severe hyperparathyroidism (NSHPT) [1; 22; 23]. Children with this condition develop severe hypercalcaemia [1; 22].

### **2.1.2.5 MEN4 (CDKN1B and potentially other CDKI-genes)**

This (OMIM 610755) has been described as a distinctive type of multiple endocrine neoplasia, and may include PHPT [16; 24]. They include mutations of the CDKN1B gene (cyclin-dependent kinase inhibitor 1B) [16; 24].

### **2.1.2.6 Rare mutations – only case reports linking these to PHPT:**

**2.1.2.6.1 Carney complex:** This requires at least two “major” criteria [lentiginoses, primary pigmented nodular adrenocortical syndrome, myxomas in heart or skin, acromegalia, testicular neoplasias, thyroid cancer] or one “major” criterion with one supplementary criterion [affected relative, PRKAR1A mutation - OMIM 160980],

**2.1.2.6.2 Cowden syndrome** [OMIM 158350, PTEN, OMIM 601728] or Cowden like syndromes [OMIM 612359] (hamartomas and an increased risk of certain cancers) [25; 26] – some overlap with HPT-JT may be seen [27].

**2.1.2.6.3 Von Hippel-Lindau (VHL) syndrome** OMIM 193300 [28]

**2.1.2.6.4 Rothmund-Thomsen syndrome** [RECQL4 – OMIM – 268400] [29]

**2.1.2.6.5 Neurofibromatosis** (NF gene, NF1 OMIM 162200, NF2 OMIM 101000) [30]

**2.1.2.6.6 Turner syndrome** (45,X) – OMIM [31]

#### **2.1.2.6.7 Gastric Carcinoid and Hyperparathyroidism syndrome (unknown gene) [32]**

**2.1.2.6.8 Primary hyperparathyroidism from watery clear cell hyperplasia (WCCH)**, where WCCH is strongly associated with bloodtype 0. There may be some overlap between syndromes, e.g. between WCCH and neurofibromatosis.

#### **2.2. External irradiation of the neck**

External irradiation of the neck has been associated with PHPT [1; 33], possibly by inducing the somatic mutations mentioned above (paragraph 2.1).

#### **2.3. Vitamin D deficiency**

Long-standing vitamin D deficiency may induce hyperplasia of the parathyroid glands. It has been hypothesized that this may stimulate autonomous functioning of one or more parathyroid glands either through generalized hyperplasia or through clonal proliferation [33]. This would then in fact be a “tertiary” hyperparathyroidism, but as it is first diagnosed in a stage with high calcium and PTH it is classified as primary hyperparathyroidism. The scope of this cause is unknown.

#### **2.4. Overweight**

Patients with primary hyperparathyroidism have a higher body weight than control patients [34]. On average a meta-analysis has suggested that the body weight is around 3.3 kg higher than in control subjects [34]. It is not known in detail if this is a causal relationship. Several hypotheses exist, but one option is that an increased amount of fat in the body alters the distribution of vitamin D, so that more of the lipophilic vitamin D is stored in the fat rather than being available in blood, bone, intestine, and kidneys. This could lead to a “functional” vitamin D deficiency leading to primary hyperparathyroidism as suggested above under item 4. Obese subjects tend to have lower serum 25-hydroxy-vitamin D than normal weight subjects [35-37], probably due to storage of vitamin D in the fat tissue leading to reduced bioavailability.

#### **2.5. Lithium**

Lithium acts as a calcilytic, i.e. it inhibits the calcium-sensing receptor (CaSR). This leads to an increased PTH secretion [38-40], as the calcium levels in blood are perceived as being too low by the CaSR. This may lead to hyperplasia of all parathyroid glands, which may turn into PHPT often affecting all parathyroid glands [41]. Little is known about the scale of the problem.

### **3. Pathogenesis:**

The pathogenesis is clonal growth of cells in single-gland adenomas and hyperplasia in multigland disease. As stated above this may be due to internal stimuli from alterations in genes controlling cell division and cycle or from external stimuli on growth (lithium, vitamin D deficiency, overweight).

Fig. 1: Growth patterns of parathyroid adenomas and hyperplasia

Fig. 1A: Parathyroid adenoma – sigmoid growth

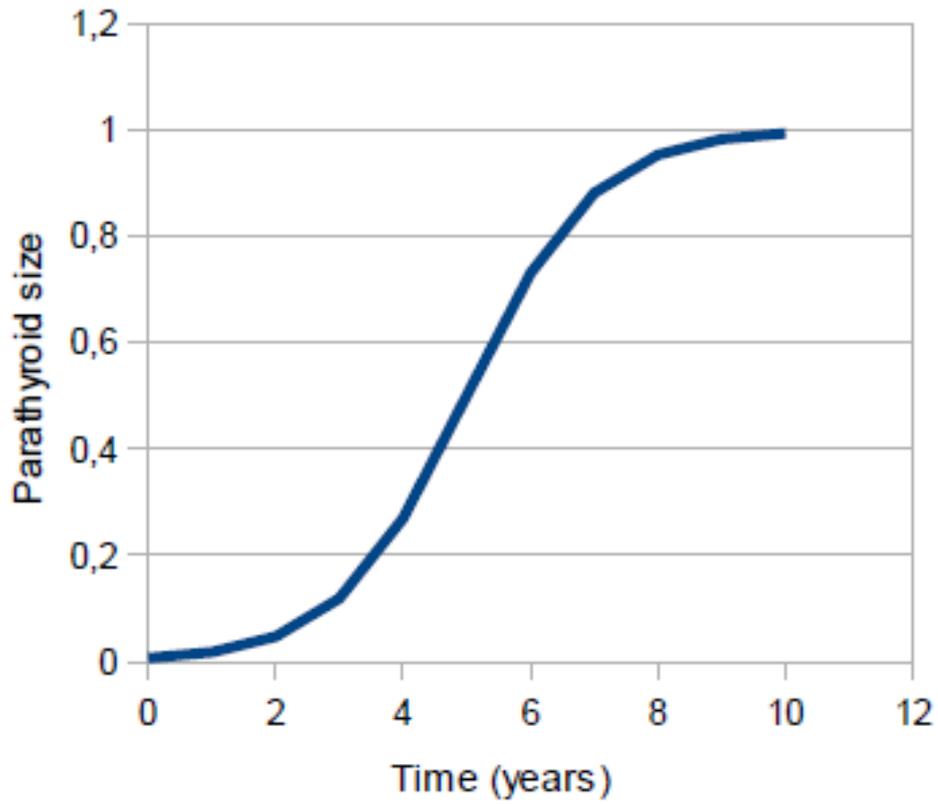
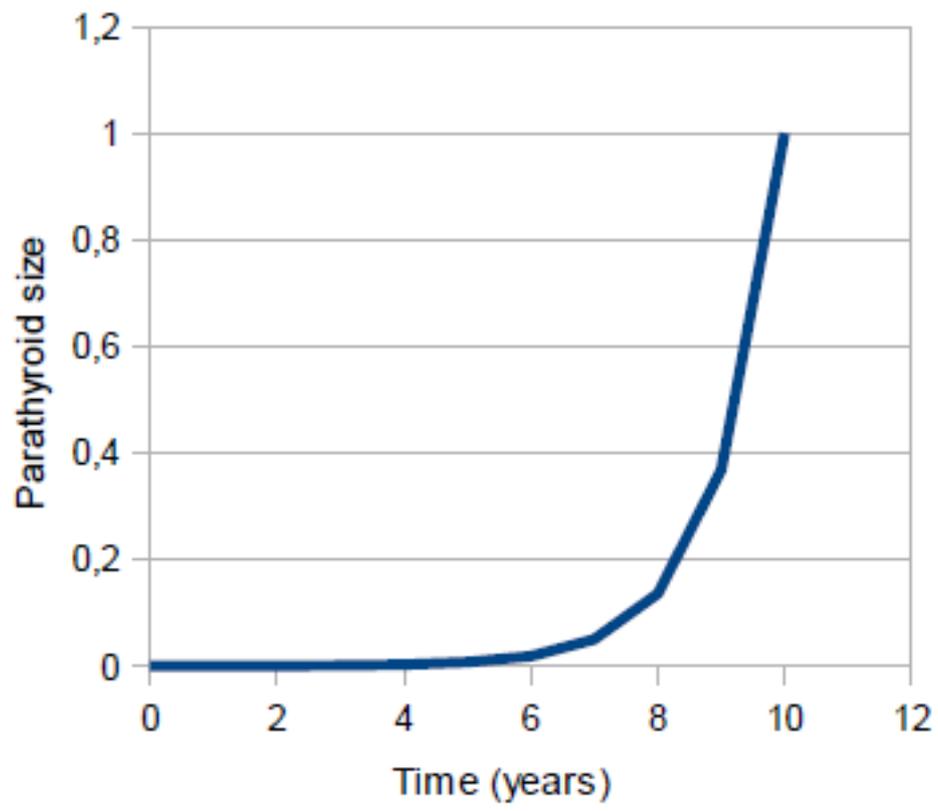


Fig. 1B: Parathyroid hyperplasia – exponential growth



## Bibliography

- [1] Arnold A, Shattuck T, Mallya S, Krebs L, Costa J, Gallagher J et al. . Molecular pathogenesis of primary hyperparathyroidism. *J Bone Miner Res* 2002; 17 Suppl 2:N30-6: N30-N36.
- [2] Pearce SH, Trump D, Wooding C, Sheppard MN, Clayton RN , Thakker RV. Loss of heterozygosity studies at the retinoblastoma and breast cancer susceptibility (BRCA2) loci in pituitary, parathyroid, pancreatic and carcinoid tumours. *Clin Endocrinol (Oxf)* 1996; 45: 195-200.
- [3] Gagel R. Multiple endocrine neoplasia. *Endocrinol Metab Clin North Am* 1994; 23(1): 1-228.
- [4] Chandrasekharappa SC, Guru SC, Manickam P, Olufemi SE, Collins FS, Emmert-Buck MR et al. . Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science* 1997; 276: 404-407.
- [5] Agarwal SK, Guru SC, Heppner C, Erdos MR, Collins RM, Park SY et al. . Menin interacts with the AP1 transcription factor JunD and represses JunD-activated transcription. *Cell* 1999; 96: 143-152.
- [6] Kassem M, Kruse TA, Wong FK, Larsson C , Teh BT. Familial isolated hyperparathyroidism as a variant of multiple endocrine neoplasia type 1 in a large Danish pedigree. *J Clin Endocrinol Metab* 2000; 85: 165-167.
- [7] Bassett JH, Forbes SA, Pannett AA, Lloyd SE, Christie PT, Wooding C et al. . Characterization of mutations in patients with multiple endocrine neoplasia type 1. *Am J Hum Genet* 1998; 62: 232-244.
- [8] Lemos MC , Thakker RV. Multiple endocrine neoplasia type 1 (MEN1): analysis of 1336 mutations reported in the first decade following identification of the gene. *Hum Mutat* 2008; 29: 22-32.
- [9] Turner JJO, Leotlela PD, Pannett AAJ, Forbes SA, Bassett JHD, Harding B et al. . Frequent occurrence of an intron 4 mutation in multiple endocrine neoplasia type 1. *J Clin Endocrinol Metab* 2002; 87: 2688-2693.
- [10] Chanson P, Cadiot G , Murat A. Management of patients and subjects at risk for multiple endocrine neoplasia type 1: MEN 1. GENEM 1. Groupe d'Etude des Néoplasies Endocriniennes Multiples de type 1. *Horm Res* 1997; 47: 211-220.
- [11] Akerström G , Stålberg P. Surgical management of MEN-1 and -2: state of the art. *Surg Clin North Am* 2009; 89: 1047-1068.
- [12] Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H et al. . Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid* 2009; 19: 565-612.
- [13] Vestergaard P, Kroustrup J, Rønne H, Eng C , Laurberg P. Neuromas in multiple endocrine neoplasia type 2A with a RET codon 611 mutation. *J Endocrine Genetics* 1999; 1: 33-37.
- [14] Masi G, Barzon L, Iacobone M, Viel G, Porzionato A, Macchi V et al. . Clinical, genetic, and histopathologic investigation of CDC73-related familial hyperparathyroidism. *Endocr Relat Cancer* 2008; 15: 1115-1126.
- [15] Simonds WF, James-Newton LA, Agarwal SK, Yang B, Skarulis MC, Hendy GN et al. . Familial isolated hyperparathyroidism: clinical and genetic characteristics of 36 kindreds. *Medicine (Baltimore)* 2002; 81: 1-26.
- [16] Vierimaa O, Villablanca A, Alimov A, Georgitsi M, Raitila A, Vahteristo P et al. . Mutation analysis of MEN1, HRPT2, CASR, CDKN1B, and AIP genes in primary hyperparathyroidism patients with features of genetic predisposition. *J Endocrinol Invest* 2009; 32: 512-518.
- [17] Iacobone M, Barzon L, Porzionato A, Masi G, Macchi V, Marino F et al. . Parafibromin expression, single-gland involvement, and limited parathyroidectomy in familial isolated hyperparathyroidism. *Surgery* 2007; 142: 984-91; discussion 984-91.
- [18] Iacobone M, Masi G, Barzon L, Porzionato A, Macchi V, Ciarleglio FA et al. . Hyperparathyroidism-jaw tumor syndrome: a report of three large kindred. *Langenbecks Arch Surg*

2009; 394: 817-825.

- [19] Newey PJ, Bowl MR, Cranston T, Thakker RV. Cell division cycle protein 73 homolog (CDC73) mutations in the hyperparathyroidism-jaw tumor syndrome (HPT-JT) and parathyroid tumors. *Hum Mutat* 2010; 31: 295-307.
- [20] Sarquis MS, Silveira LG, Pimenta FJ, Dias EP, Teh BT, Friedman E et al. . Familial hyperparathyroidism: surgical outcome after 30 years of follow-up in three families with germline HRPT2 mutations. *Surgery* 2008; 143: 630-640.
- [21] Christensen SE, Nissen PH, Vestergaard P, Heickendorff L, Brixen K, Mosekilde L. Discriminative power of three indices of renal calcium excretion for the distinction between familial hypocalciuric hypercalcaemia and primary hyperparathyroidism: a follow-up study on methods. *Clin Endocrinol (Oxf)* 2008; 69: 713-720.
- [22] Bai M, Janicic N, Trivedi S, Quinn SJ, Cole DE, Brown EM et al. . Markedly reduced activity of mutant calcium-sensing receptor with an inserted Alu element from a kindred with familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. *J Clin Invest* 1997; 99: 1917-1925.
- [23] Pearce SH, Trump D, Wooding C, Besser GM, Chew SL, Grant DB et al. . Calcium-sensing receptor mutations in familial benign hypercalcemia and neonatal hyperparathyroidism. *J Clin Invest* 1995; 96: 2683-2692.
- [24] Buchwald PC, Akerström G, Westin G. Reduced p18INK4c, p21CIP1/WAF1 and p27KIP1 mRNA levels in tumours of primary and secondary hyperparathyroidism. *Clin Endocrinol (Oxf)* 2004; 60: 389-393.
- [25] Hamby LS, Lee EY, Schwartz RW. Parathyroid adenoma and gastric carcinoma as manifestations of Cowden's disease. *Surgery* 1995; 118: 115-117.
- [26] Kreisman H, Robitaille Y, Dionne GP, Palayew MJ. Lymphangiomyomatosis syndrome with hyperparathyroidism: a case report. *Cancer* 1978; 42: 364-372.
- [27] Teh BT, Farnebo F, Kristoffersson U, Sundelin B, Cardinal J, Axelson R et al. . Autosomal dominant primary hyperparathyroidism and jaw tumor syndrome associated with renal hamartomas and cystic kidney disease: linkage to 1q21-q32 and loss of the wild type allele in renal hamartomas. *J Clin Endocrinol Metab* 1996; 81: 4204-4211.
- [28] Arao T, Okada Y, Tanikawa T, Inatomi H, Shuin T, Fujihira T et al. . A case of von Hippel-Lindau disease with bilateral pheochromocytoma, renal cell carcinoma, pelvic tumor, spinal hemangioblastoma and primary hyperparathyroidism. *Endocr J* 2002; 49: 181-188.
- [29] Werder EA, Mürset G, Illig R, Prader A. Hypogonadism and parathyroid adenoma in congenital poikiloderma (Rothmund-Thomson syndrome). *Clin Endocrinol (Oxf)* 1975; 4: 75-82.
- [30] Altinova AE, Toruner F, Cimen AR, Karakoc A, Atasever T, Yetkin I et al. . The association of neurofibromatosis, bilateral pheochromocytoma and primary hyperparathyroidism. *Exp Clin Endocrinol Diabetes* 2007; 115: 468-470.
- [31] Paul TV, Dinakar J, Thomas N, Mathews SS, Shanthly N, Nair A. A case of Turner syndrome with hyperparathyroidism in an adult. *Ear Nose Throat J* 2008; 87: 110-112.
- [32] Christopoulos C, Balatsos V, Rotas E, Karoumpalis I, Papavasileiou D, Kontogeorgos G et al. . The syndrome of gastric carcinoid and hyperparathyroidism: a family study and literature review. *Eur J Endocrinol* 2009; 160: 689-694.
- [33] Adami S, Marcocci C, Gatti D. Epidemiology of primary hyperparathyroidism in Europe. *J Bone Miner Res* 2002; 17 Suppl 2:N18-23: N18-N23.
- [34] Bolland M, Grey A, Gamble G, Reid I. Association Between Primary Hyperparathyroidism and Increased Body Weight: A Meta-Analysis. *J Clin Endocrinol Metab* 2004; 90: 1525-1530.
- [35] Bell N, Epstein S, Greene A, Shary J, Oexmann M, Shaw S. Evidence for alteration of the vitamin D-endocrine system in obese subjects. *J Clin Invest* 1985; 76: 370-373.
- [36] Margiloff L, Harris S, Lee S, Lechan R, Dawson-Hughes B. Vitamin D status of an outpatient clinic population. *Calcif Tissue Int* 2001; 69: 263-267.

- [37] Need A, Morris H, Horowitz M , Nordin C. Effects of skin thickness, age, body fat, and sunlight on serum 25-hydroxyvitamin D. *Am J Clin Nutr* 1993; 58: 882-885.
- [38] Brown E. Lithium induces abnormal calcium-regulated PTH release in dispersed bovine parathyroid cells. *J Clin Endocrinol Metab* 1981; 52: 1046-1048.
- [39] Seely E, Moore T, Leboff M , Brown E. A single dose of lithium carbonate acutely elevates intact parathyroid hormone levels in humans. *Acta Endocrinol (Copenh)* 1989; 121: 174-176.
- [40] Nordenstrom J, Elvius M, Bagedahl-Strindlund M, ZHAO B , Torring O. Biochemical hyperparathyroidism and bone-mineral status in patients treated long-term with lithium. *Metabolism* 1994; 43: 1563-1567.
- [41] Stancer H , Forbarh N. Hyperparathyroidism, hypothyroidism, and impaired renal function after 10 to 20 years of lithium treatment. *Arch Intern Med* 1989; 149: 1042-1045.