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Cardiovascular abnormalities in primary hyperparathyroidism

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ABSTRACT

Primary hyperparathyroidism is the third most frequent endocrinopathy. Its prevalence and incidence vary in the different regions of the world. In the last 30 years, detection has been more frequent, and four consensuses have been reported, the last one in 2013. It was published in Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop. It mentions eight indications to be able to carry out a parathyroidectomy. The consensuses differ very little in the indications. In patients with this ailment, cardiovascular morbidity has increased. After having checked some cardiovascular abnormalities (systemic arterial hypertension, arrhythmias, left ventricular hypertrophy, aorta valve calcification, and other abnormalities), we suggest that arterial hypertension, left ventricular hypertrophy, and arrhythmias be considered as indications to undergo parathyroidectomy. (REV MEX ENDOCRINOL METAB NUTR. 2015;2:204-8)

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RESUMEN

El hiperparatiroidismo primario es la tercera endocrinopatía más frecuente. Su incidencia y prevalencia varían en las diferentes regiones del mundo. En los últimos 30 años su detección ha sido más frecuente. Se han reportado cuatro consensos, el último en el 2013, publicando el *Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop*, donde se mencionan las ocho indicaciones para realizar paratiroidectomía. Los consensos difieren muy poco en las indicaciones quirúrgicas. En estos pacientes ha aumentado la mortalidad cardiovascular. Después de hacer una revisión de las anormalidades cardiovasculares: hipertensión arterial sistémica, arritmias, hipertrofia ventricular izquierda, calcificación valvular aórtica y otras anormalidades, sugerimos que la hipertensión arterial, hipertrofia ventricular izquierda y arritmias sean consideradas indicaciones de paratiroidectomía.

Palabras clave: Hiperparatiroidismo. Cardiovascular.

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INTRODUCTION

Castleman and Mallory established, for the first time in 1935, that primary hyperparathyroidism etiology was parathyroid adenomas[1]. Currently, diabetes mellitus, osteoporosis, and primary hyperparathyroidism (PHPT) are the most common endocrinopathies[2]. The PHPT etiologies are: 75-85% one adenoma, 2-12% two adenomas, multi-glandular hyperplasia 10-15%, carcinoma < 1%[3-5]. Primary hyperparathyroidism is a pathology characterized by the excessive biosynthesis and secretion of the parathyroid hormone, concomitant with hypercalcemia, and/or normocalcemia. The definite diagnosis is the histopathologic study of the main cells of the parathyroid glands.

EPIDEMIOLOGY

Primary hyperparathyroidism affects approximately 1% of the American population. Its incidence is three times greater in the female gender compared to the male gender. Prevalence and incidence may vary in the different regions of the world, and with the different ethnic, age, and gender groups. Prevalence in the population in general is about 3-7 cases for 1,000 adults[6-8]. Incidence has been estimated to be between 0.4 to 21.6 cases per 100,000 people a year[9]. Morbidity rate is reported to be, in several countries, 0.35 per million people a year.

OBJECTIVE

The increment of mortality and/or morbidity due to cardiovascular problems in PHPT is analyzed. These cardiovascular alterations, which are developed in primary hyperthyroidism and are not included in The Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop[10], are discussed.

Table 1. Primary hyperparathyroidism diagnosis criteria

↑ Parathyroid hormone whole
Hypercalcemia; 1 mg upper limit normal and*
Calcium 2+ high
Hypophosphatemia
1,25 dihydroxy vitamin D decreased
Hypomagnesemia
Nephrolithiasis and/or nephrocalcinosis
Bone disease: osteoporosis†, fractures‡
Hyperuricemia and gout/pseudogout
Proximal renal tubular acidosis
Normochromic, normocytic anemia
Phosphatase alkaline
Albumin

*Hypercalcemia must be corrected according to albumin concentration; †Lumbar spine, total hip, neck femoral or distal 1/3 radius; ‡Vertebral fracture, neck femoral, total hip or distal 1/3 radius.
‡n = 19.

Primary hyperthyroidism manifestations in the organism are multi-systemic and heterogeneous. Nephrolithiasis is found in 15-20% of patients with PHPT[11]. Five percent of the patients with renal lithiasis present PHPT[12], but nephrocalcinosis is uncommon in these patients[13]. Complications on the cortical bone tissue are more frequent (Ward triangle and radio third lower) than the trabecular bone (lumbar backbone). There is a decrease in mineral bone density that results in osteoporosis and fracture[14-16].

The Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop[10]; Criteria for carrying out parathyroidectomy (Table 1):

1. Serum calcium > 1 mg over the upper normal limit (corrected through the albumin concentration);
2. Densitometry with:
   - a) T score < 2.5 in the lumbar backbone, Ward triangle and radius third distal;
   - b) Backbone fracture identified by abdominal X-ray, computed tomography, magnetic resonance imaging;
3. Creatinine clearance < 60 ml/min;

4. a). Hypercalciuria urine 24 h > 400 mg.

4. b). Nephrolithiasis and/or nephrocalcinosis;

5. Age < 50 years.

Cardiovascular manifestations

Systemic arterial hypertension

Morbidity and mortality are greater in patients with PHPT. It has been informed recently that arterial hypertension is found in 40-65% of patients with PHPT[17-20].

Physiopathology is carried out through the following mechanisms: (i) sympathetic system hyperactivity and/or angiotensin-renin-aldosterone system; (ii) dysfunction or structural modifications of the resistance vessels by a decreased vasodilator response20,21.

Vascular endothelium is an endocrine gland with a large tissue mass. It is formed by a diversity of endothelial cell population, which is heterogeneous in its morphology and physiology, forming the great endothelium structure in the organism. It has the function of keeping the basal vascular tone; this vasodilation depends on the endothelium and the integrity of the structural architecture of the vascular wall through biosynthesis and release of nitric oxide (NO^-). This diatomic radical diminishes the atherothrombosis genesis and has a multi-function on the different tissues of the organism. Endothelial cell dysfunction leads to a decrease on the NO^- production. This radical is deactivated by the reactive oxygen species. The interaction between $NO^- + O_2^- \rightarrow$ peroxynitrite ($ONOO^-$) is associated to the essential hypertension genesis. The endothelium synthetizes another vessel-relaxant molecule: endothelium-derived hyperpolarizing factor (EDHF). This molecule induces vasodilation by hyperpolarizing smooth muscle cells as a rapid compensatory pathway[23]. The cytochrome enzymatic system P450 epoxygenase (CYP2C9) is found in the endothelial cells, and possibly has been associated with hyperpolarizing factor biosynthesis derived from the endothelium at the peripheral microcirculation of the patients with essential hypertension[24].

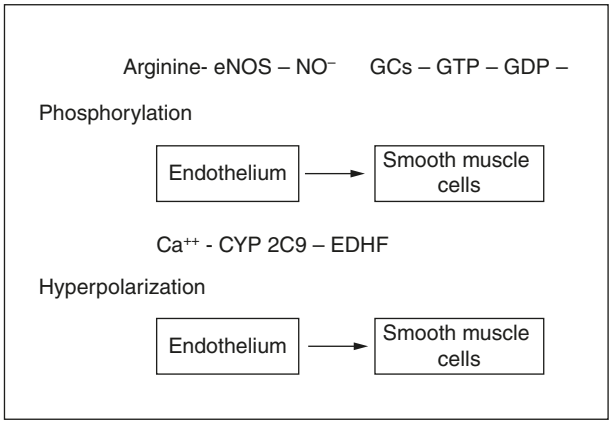

Figure 1. eNOS: endothelial nitric oxide synthase; NO: nitric oxide; GC: guanylate cyclase; GTP: guanosine triphosphate; GDP: guanosine diphosphate; Ca: calcium; EDHF: endothelium-derived hyperpolarizing factor.

Research on endothelium-dependent vasodilation has shown alterations in PHPT, though there are certain controversies. The body of knowledge supports the hypothesis that alterations in the endothelium are implicated in the process. It is considered that the complex NO^-, O_2^- and EDHF is possibly associated in the hypertension genesis. However, recent data on relaxation mediators dependent on the endothelium is being researched. Vasodilation in PHPT is decreased via NO^- biosynthesis. This process would be compensated by EDHF biosynthesis. (Fig. 1).

Electrocardiographic alterations

Hypercalcemia produces a constellation of electrocardiographic abnormalities: shortening of QT interval frequently associated with the enlargement of PR interval, and a longer duration of QRS[25].

It has been proposed that interval QT corrected measurement (cQT) is a predictor of mortality. It is known that the altered action potential duration is the generator of arrhythmias as presented in the cQT and/or long QT. Arrhythmias in hypercalcemia can be produced after initial or late ventricular depolarization.[26] This condition is present particularly in sinus tachycardia and premature ventricular contractions; the reflection is that hypercalcemia affects the potential action duration in phase 2 of plateau,

and that it diminishes the ventricular contraction speed and shortens the refractory period of the ventricle may be true. The combination of these abnormalities produces triggered activity phenomena, which frequently produce reentry arrhythmias. Furthermore, PHPT, frequently, evolves with left ventricular hypertrophy, which is the perfect ground for ventricular reentry phenomena. Ionized calcium penetrates the intercellular area through L-type Ca^{++} channels with every potential action stimulating the release of calcium. This is done from the sarcoplasmic reticulum going through type 2 ryanodine receptor channels. The kinetics of cytosolic Ca^{++} in diastole is transported through sarcoplasmic reticulum by means of the (Na^{+})-Ca^{++} channel; Ca^{++} travels again to the citosol, and then an increased exchanger function underlies the delays after polarizations in patients with chronic atrial fibrillation, which may be also the mechanism that underlie the arrhythmias in patients with PHPT[27].

It is probable that the stress associated to the increased sympathetic tone (a condition which is also produced by hyperparathyroidism) increases the potential risk of arrhythmia and mortality. This is why a basal electrophysiological study with sympathetic mimetic drugs should be carried out to reproduce potential malignant arrhythmias in vulnerable patients with PHPT. The range of electrical disturbances evoked by a set of channelopathies includes Ca^{++} channels. These, when increasing or reducing their intracellular kinetics, may increase Ca^{++} generating abnormal electrocardiographic patterns, which may be another marker of potential arrhythmias like the Brugada electrocardiographic pattern type 128.

Echocardiographic alterations

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is a strong predictor for cardiovascular mortality in patients with PHPT in most of the cases[29-34]. It has been suggested that arterial hypertension in many PHPT patients increases the possibility of LVH, and it may be attributed to arterial hypertension. However, it has been considered that LVH is independent from hypertension[32]. The mass of evidence sustains that the association of LVH with parathyroid hormone (PTH) and hyperparathyroidism (HP) concentrations is meaningful[29-31]. It has also been reported as a factor for association of Ca^{++} concentration and LVH. It is likely that PTH and Ca^{++} increase are responsible for LVH, and it may be the cause of developing cardiovascular stiffness in HP. Other data that supports this argument is the reversibility of the cardiovascular anomalies six months after parathyroidectomy. The exact mechanism of action has not been established. The hypothesis proposed is that when PTH interacts with the PTH receptor at the cardiomiocito, intracellular Ca^{++} is increased. This action relaxes the protein enzyme kinase C, which participates in protein biosynthesis with function kinase and no kinase generating cellular hypertrophy and leads to LVH. Two-dimensional transthoracic echocardiogram can measure the diastolic diameter, thickening of the interventricular septum of the posterior wall. Left ventricular mass was calculated. It was abnormal in women; the figures were 108 g/cm^2 for women and 131 g/cm^2 in men.

Aortic valve calcification

Aortic valve calcification represents an early atherosclerotic change that can lead to an aortic valve stenosis[36], which constitutes an independent factor for cardiovascular mortality[37]. Aortic valve calcification process is associated with PHPT concentration[38]. Iwata, et al. studied a group of 51 patients with asymptomatic PHPT with hypercalcemia > 10.2 mg/dl < 12 mg/dl and increased PTH. This assay showed a calcification area of 41% in HP patients compared to the control ones. Parathyroid hormone is fundamental in osteoblastic activity. Aortic valve calcification is an active process similar to osteogenesis that implies the osteoblastic transformation of the valve apparatus[39,40]. Another related factor is the mechanical stress due to the flow that is handled with this valve, which is different to the mitral tricuspid valves.

Other cardiovascular abnormalities presented in PHPT are diastolic dysfunction, coronary artery disease with silent or symptomatic ischemia, cardiomyocyte calcification, and endothelial dysfunction.

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