Musculoskeletal manifestations in primary hyperparathyroidism

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ABSTRACT

Objective: To evaluate the musculoskeletal manifestations of primary hyperparathyroidism (PHP). **Patients and methods:** Clinical, with emphasis on musculoskeletal manifestations, laboratorial, and densitometric data of 21 PHP patients followed-up in our service were evaluated. **Results:** Only post-menopausal patients, with mean age of 67.9 ± 11.2 years, of which 16 (76.2%) were Caucasian, participated in this study. Serum levels of calcium, phosphorus, 25 hydroxy vitamin D, and parathyroid hormone (PTH) at the time of diagnosis were 10.6 ± 0.9 mg/dL, 2.9 ± 0.7 mg/dL, 16.6 ± 6.6 ng/mL, and 113.7 ± 74.8 pg/mL, respectively. Thirteen (61.9%) patients had osteoarthritis, 7 (33.3%) diffuse arthralgia, 6 (28.6%) diffuse myalgia, 3 (14.3%) chondrocalcinosis, and 2 (14.3%) tendinopathy. Half of 14 (67.8%) patients with osteoporosis had a history of bone fracture (2 of the distal radius, 4 of the vertebral spine, 2 of the fingers, and 2 of the ankles). Eleven (52.4%) patients had hypertension, 5 (23.8%) hypothyroidism, 4 (18.0%) peptic ulcer, 3 (14.3%) kidney stones, 2 (9.5%) depression, and 2 (9.5%) psoriasis. Fifteen patients (71.4%) underwent parathyroidectomy, seven had a diagnosis of adenoma of the parathyroid, and an improvement of the symptoms was observed in 61.5% of those patients. **Conclusions:** Primary hyperparathyroidism has variable clinical manifestations in which musculoskeletal symptoms predominate. Knowledge of this disorder and its inclusion in the differential diagnosis of rheumatic diseases allows the early diagnosis, therefore minimizing clinical complications.

Keywords: comorbidities, primary hyperparathyroidism, musculoskeletal manifestation, osteoporosis.

INTRODUCTION

Primary hyperparathyroidism (PHP) is a metabolic disorder secondary to autonomous hyperfunction of one or more of the parathyroid[1] glands, resulting in a progressive increase in the serum level of the parathyroid hormone (PTH) and calcium.

Primary hyperparathyroidism has a prevalence of 1-4 in 1,000 individuals, affecting women more often (3 women:1 man), with a peak between 50 and 60 years of age.[2-4]

Adenoma in one of the glands is the most common etiology,[2] affecting approximately 85% of the patients.[5] Less frequently, an increase in the size of two glands, or even diffuse hyperplasia,[5] is seen, and parathyroid carcinoma is a rare disorder.[4]

The majority of the patients have a subtle increase in PTH and calcium levels and they are asymptomatic;[6] consequently, the history and physical exam rarely provide any indications of PHP. In less than half of the cases, PHP can present with different clinical manifestations secondary to hypercalcemia. Therefore, those patients can present with kidney stones and nephrocalcinosis, hypertension, arrhythmias, diabetes mellitus, peptic ulcer, constipation, psychiatric changes,

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such as depression, and cognitive changes. Among malignat neoplasias, which are present in 1-4% of the cases, types 1 and 2 multiple endocrine neoplasia should be mentioned.[1,4,7-16]

Symptoms of fibromyalgia, muscular weakness, fatigue, myalgia, arthralgia, pseudogout, and chondrocalcinosis are among the musculoskeletal manifestations.[17-19] Metabolically, bone pain, osteoporosis in advanced cases, and fibrous cystic osteitis are seen. Epidemiological studies suggest that the risk of fractures, due to fragility of the skeleton, is increased in patients with PHP.[20,21]

In order to evaluate the magnitude of the musculoskeletal manifestations and comorbidities in PHP, we analyzed patients with this diagnosis followed-up at the Osteometabolic Disorders Clinic of the Rheumatology Department of the Hospital das Clínicas of the Medical School of the University of São Paulo (HC/FMUSP), a tertiary service.

PATIENTS AND METHODS

A retrospective evaluation of the musculoskeletal manifestations and comorbidities of all PHP patients followed-up at the Osteometabolic Diseases Clinic (HC/FMUSP) from 2001 to 2009 was undertaken. Demographic, clinical, laboratorial, and densitometric data were collected from the medical records of the patients. The densitometric and laboratorial data at the time of the diagnosis of PHP were used.

The diagnosis of PHP was based on the presence of hypercalcemia (>10.4 mg/dL) and increased levels of PTH[4]. Serum levels of PTH were determined by immunochemiluminometric assay with normal reference values (RV) of 16 to 87 pg/mL. Serum (RV:8.4-10.2 mg/dL) and urinary calcium levels, as well as serum phosphate (RV: 2.5-4.5 mg/mL) were determined by automated colorimetric enzymatic technique. Alkaline phosphatase (RV: 35-104 Ul) levels were determined by automated kinetic assay. Levels of 25 hydroxy vitamin D (25OHD) were determined by radioimmunoassay (DiaSorin, Minnesota, USA). Those exams were routinely done on the day before the clinic appointment.

Diagnosis of comorbidities: (a) osteoarthritis: according to the criteria of the American College of Rheumatology;[22] (b) osteoporosis: according to the criteria of the world Health Organization;[23] (c) hypertension: III Brazilian Consensus on Hypertension;[24] (d) hypothyroidism: based on elevated levels of TSH (RV: 0.38-4.5 mIU/mL) and reduction in free T4 (RV: 0.8-2.3 ng/dL); (e) depression: according to the Diagnostic and Statistical Manual of Mental Disorders.[25]

RESULTS

From 2001 to 2009, 900 patients were evaluated at the Osteometabolic Disorders Clinic of HC-FMUSP. The majority of those patients were referred to our service with suspected osteoporosis. Out of 900 patients, 21 (2.3%) were diagnosed with PHP in our service. They were all post-menopausal females and 16 (76.2%) were Caucasian. Patients had a mean age of 67.9 ± 11.2 years, ranging from 44 to 88 years, while the mean age of menopause was 50.3 ± 4.4 years. Mean body mass index was 29.1 ± 4.4 kg.m^2.

Table 1 shows the musculoskeletal manifestations and comorbidities that could be related to primary hyperparathyroidism. All 21 patients had at least one musculoskeletal manifestation. Eight of them (38.1%) did not have osteoarticular manifestations. Chronic renal failure, gout, and multiple endocrine malignancies (type 1 or 2) were not observed. All patients had a sedentary lifestyle, they did not have a history of smoking, alcoholism, and use of glucocorticoids, and half of them were on hormone replacement therapy.

Table 1. Musculoskeletal manifestations and other comorbidities in 21 patients with primary hyperparathyroidism

Manifestation	Cases (%)
Osteoarthritis	13 (61.9)
Diffuse arthralgia	7 (33.3)
Diffuse myalgia	6 (28.6)
Chondrocalcinosis	3 (14.3)
Tendinopathy	2 (9.5)
Osteoporosis	14 (66.6)
Osteopenia	5 (23.8)
Fracture	7 (33.3)
Hypertension	11 (52.4)
Hypothyroidism	5 (23.8)
Peptic ulcer	4 (18.0)
Kidney Stones	3 (14.3)
Depression	2 (9.5)
Psoriasis	2 (9.5)

As for osteometabolic changes, 14 (67.8%) patients had osteoporosis and five (23.8%) had osteopenia diagnosed by bone densitometry (Table 1). Mean mineral bone density (MBD) of the lumbar spine (L1-L4) was 0.820 ± 0.194 g/cm^2 with T-score of -2.20 ± 1.79. In the femoral neck, MBD and T-score were 0.738 ± 0.142 g/cm^2 and 1.58 ± 1.42, respectively.

Seven (33.3%) patients had bone fractures of which two were in the distal third of the radius, four in the spine, two in the fingers, and two in the ankles (Table 1).

Serum levels of biochemical parameters were as follows: total calcium 10.6 ± 0.9 (RV: 8.4-10.2 mg/dL), phosphorus 2.9 ± 0.7 (RV: 2.5-4.5 mg/mL), alkaline phosphatase 113.7 ± 74.8 (RV: 35-104 U/l), 25OHD 16.6±6.6 (RV: 16-87 pg/mL), and intact PTH 139.5 ± 59.9 (RV: 16-87 pg/mL), and urine calcium 4.4 ± 2.6 mg.kg in 24 hours, and hypercalciuria was observed in 12 (57.1%) patients.

In face of the clinic-laboratorial findings, 20 (95.2%) patients underwent ultrasound of the parathyroid glands and/or complemented with MIBI (methoxyisobutylisonitrile) scintigraphy in 19 cases, confirming the diagnosis of PHP and localizing the affected gland(s) for surgery.

Out of 21 patients, 15 (71.4%) underwent parathyroidectomy; seven of them had evidence of parathyroid adenoma and the remaining had parathyroid hyperplasia. Seventeen out of 21 patients had already surgical indication for asymptomatic PHP: Five patients had serum calcium > 1 mg/dL above normal, five had urine calcium > 400 mg/day, 14 patients with MBD T-score <-2.5 in any site, and two were < 50 years old. Besides, bone density in eight out of 15 patients had decreased, and one had fracture despite clinical treatment. Before surgery, four out of 15 patients were being treated with antiresorbtive drugs (one on 60 mg/day of raloxifene chloride, and four on 10 mg/day of disodium alendronate). None of those patients were on hormone replacement therapy.

Six patients did not undergo parathyroidectomy for different reasons: one lost follow-up appointments, one did not have clinical conditions for surgery, one refused surgery, and three are scheduled for future parathyroidectomy.

DISCUSSION

In the present study, musculoskeletal manifestations and comorbidities that could be related with PHP were evaluated in 21 patients with this diagnosis.

As a rule, PHP is primarily asymptomatic.[1,6,26] However, in the present study, an elevated incidence of musculoskeletal manifestations was observed; more than half of the patients had signs/symptoms of osteoarthritis, one third had diffuse arthralgia, followed by symptoms of fibromyalgia, chondrocalcinosis, and tendinopathies.

Musculoskeletal symptoms can be seen in 53% of the cases.[27] Myalgia, usually diffuse, can affect 14-41% of the patients with PHP.[27-30]. In this case, fibromyalgia, which can overlap the muscular symptoms of PHP, is the main differential diagnosis. In our cohort, the symptoms of diffuse myalgia of three out of four patients improved after parathyroidectomy, while one patient required continuous drug therapy, even after surgery, because they were probably due to fibromyalgia.

Arthralgia, affecting mainly large joints, is present in 32% of the patients with PHP.[27] The differential diagnosis would be with primary osteoarthritis. In the present study, generalized arthralgia in three patients with knee osteoarthritis improved after parathyroidectomy.

Chondrocalcinosis can affect 18-40% of the patients with PHP.[30,31] This is a radiographic finding associated with this disorder.

A high incidence of osteometabolic manifestations, such as osteoporosis and bone fractures, was also observed. Primary hyperparathyroidism is associated with a reduction in MBD, especially in the cortical bone, such as in the distal third of the radius.[32,33] In the lumbar region, composed mainly by trabecular bone, and in the femoral region, composed by cortical and trabecular bone, the reduction in MBD is less severe[32-34] or preserved.[35] In severe cases of PHP, a significant reduction in MBD can be seen in all types of bones.[1] In the present study, densitometry of the spine and hips, obtained at the time of the diagnosis of PHP, were analyzed. Densitometry data specific for the distal third of the radius was not available for evaluation. Despite this, a high incidence of osteoporosis was diagnosed in the lumbar and femoral regions, demonstrating that we might be dealing with patients with severe PHP. On the other hand, osteoporosis could be partly explained by the profile of the patients: post-menopausal women and, in half of the cases, without hormone replacement therapy.

The diagnosis or association of secondary hyperparathyroidism was ruled out in the present study, since all patients had elevated serum levels of calcium and normalization of PTH after the surgery to remove the parathyroid(s).

As for clinical comorbidities in PHP, hypertension can be seen in 10 to 40% of the cases.[36-38] In the present study, more than half of the patients had high blood pressure. This could be due to the synthesis of parathyroid hypertensive factor[37] triggering an increase in blood pressure in those patients. The increase in PTH is also associated with disruption in the renin-angiotensin-aldosterone system. Besides, the increased inflow of calcium in the smooth muscle cells of the blood

vessels, mediated by vitamin D, causes an increase in vascular resistance and blood pressure.[39]

The coexistence or not of PHP and hypothyroidism is controversial[40-42]. The majority of the reports is based on case reports or non-controlled studies. Regal *et al*.[41] observed, in 54 consecutive cases of PHP, 52% of cases of thyroid disease, but hypothyroidism was seen in only two cases. In the present study, four (19.0%) cases of hypothyroidism were observed.

The incidence of dyspeptic symptoms in PHP is relatively high (22.8%).[43] Clinically, nausea, vomiting, and abdominal pain can be observed.[43-45] The incidence of peptic ulcers is increased in PHP, and this could be due to an increase in the secretion of gastric acid.[45] In the population of the present study, four (19.0%) patients had peptic ulcers.

Among the renal manifestations of PHP, kidney stones affect 15-20% of the cases.[1] Hypercalciuria, affecting 40% of the patients, nephrocalcinosis, and a reduction in creatinine clearance, whose incidence is unknown, can also be seen.

Non-specific signs or symptoms, such as fatigue, anxiety, depression, or neurologic and cognitive disorders, can also be seen in PHP.[46,47] Depression usually affects 10% of the cases, and such was the case of the present study. Those signs and symptoms can overlap symptoms of fibromyalgia, which, as mentioned before, can also be seen in patients with PHP.

Parathyroidectomy can reduce the symptoms of depression, improving the quality of life, as well as reducing or eliminating the use of antidepressants in approximately half of the cases.[46]

Until now, only one case of association of hyperparathyroidism, renal osteodystrophy, and psoriatic arthritis has been reported in the literature.[48] However, the association between PHP and psoriasis has not been reported. In the present study, two patients with this association were seen. They had psoriasis and psoriatic arthritis, respectively, and increased PTH levels were detected during routine investigation of osteoporosis.

Approximately half of the patients who underwent parathyroidectomy had parathyroid adenoma, and the laboratorial profile improved after the surgery. The indication of surgery was based on the following criteria:[49] (a) asymptomatic patients; (b) osteoporosis on bone densitometry, i.e., T-score below -2.5 SD in one of the following sites: lumbar spine, neck of the femur, or distal radius; and/or (d) serum calcium levels more than 1 mg/dL above reference levels. Besides, (e) the presence of fractures during clinical treatment was also added.

The limiting factor of the present retrospective study was the lack of systematic evaluation of musculoskeletal symptoms and, therefore, their incidence was probably underestimated.

Summarizing, PHP has a variable clinical presentation in which musculoskeletal symptoms predominate, and it should be always remembered as one of the causes of rheumatologic manifestations. The knowledge of this disorder and its inclusion in the differential diagnosis of rheumatologic disorders allow early diagnosis and, therefore, minimize clinical complications.

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