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Monocentric experience of primary hyperparathyroidism surgery in Algeria

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ABSTRACT

Introduction: Primary hyperparathyroidism (PHPT) remains a relatively underdiagnosed disease in developing countries. The aim of this study was to assess the demographic, pathological, biochemical, and surgical characteristics of patients with primary hyperparathyroidism in a university hospital department of otolaryngology in eastern Algeria.
Materials and method: We performed a retrospective analysis of the records of 62 patients operated in our department for primary hyperparathyroidism between January 2002 and December 2013.
Results: The mean age was 47.7 ± 15 years with a female preponderance (88.7%). The mode of discovery was during a biological assessment for bone syndrome in 42% of cases. The mean calcemia was 2.92 ± 0.6 mmol/L, and the intact serum parathyroid hormone was 867.78 ± 954.50 pmol/L. A total of 54.8% of patients had bilateral neck exploration, and 45.2% had minimally invasive open parathyroidectomy. Postoperative complications were dominated by severe hypocalcemia and hungry bone syndrome.
Conclusion: The diagnosis of primary hyperparathyroidism in our country is late, and management is often performed after the appearance of bone and renal complications.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a disorder characterized by an excessive secretion of parathyroid hormone (PTH) that is inappropriate to the value of calcemia. It is related to single parathyroid adenoma in 85% of cases and to diffuse hyperplasia of the four glands in 15% of cases. Parathyroid carcinoma is very rarely involved. Over the past 40 years or so, the apparent epidemiology of PHPT has changed drastically. From a very rare disease, it has become a frequent disease with a prevalence of 1/1000 [1]. This endocrinopathy is the third most common endocrine disorder after diabetes and thyroid disorders [2], especially in women. The prevalence of PHPT has been reversed since the advent of automated blood calcium measurements in the 1970s, which made it possible to diagnose PHPT at an asymptomatic stage. This is the case in developed countries, as opposed to developing countries where the disease is still underdiagnosed and its management is only carried out after the appearance of bone and renal complications.

Little data are available on the epidemiology and characteristics of parathyroid disease in Algeria. Thus, this study aimed to assess the demographic, clinical, paraclinical, and surgical characteristics of patients with PHPT in the otolaryngology department of a university hospital in eastern Algeria.

MATERIALS AND METHODS

This is a retrospective analysis extracted from the medical records of patients operated in our department for PHPT between January 2002 and December 2013. We included all patients with biologically proven PHPT (whose diagnosis was based on criteria including hypercalcemia and/or an increase in PTH level or a normocalcemia, with an inappropriate level of PTH) and fulfilling the operability criteria of the National Institutes of Health [3]. We excluded 14 patients, those with unusable records due to lack of information (9 patients), others whose diagnosis was uncertain (3 patients), and those with parathyroid incidentalomas (2 patients). Each treated patient was investigated in the following mode: anamnesis; clinical examination; and biological exploration including at least calcemia, parathormonemia, phosphoremia, alkaline phosphatase, and albuminemia. Corrected serum calcium (cCa) was calculated using the following formula: corrected calcemia (mmol/L) = total calcemia (mmol/L) + 0.02 × [40 – albuminemia (g/L)].

Preoperative imaging studies included routine skeletal x-rays, measure of bone mineral density (BMD) using dual-energy x-ray absorptiometry, renal ultrasound, and echocardiography, as well as localization examinations, including at least a neck ultrasound (US)

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and 99mTc-sestamibi scintigraphy imaging (MIBI). Computed tomography and magnetic resonance imaging were requested in the context of persistent or recurrent hyperparathyroidism if results of US and MIBI were negative or in case of giant lesions with mediastinal extension.

Two surgical techniques were adopted. The classic approach using bilateral neck exploration (BNE) was used in the following situations: choice of surgeon, PHPT due to hyperplasia, PHPT associated with nodular thyroid disease, and PHPT with negative results of the US–MIBI couple. Minimally invasive open parathyroidectomy (MIOP) was adopted in the following situations: sporadic HPP, absence of thyroid nodules on US, and preoperative imaging in favor of single gland disease. In this technique, we do not use intraoperative parathyroid hormone monitoring.

Regarding follow-up, patients were reviewed at 1, 3, and 6 months postoperatively. A biological assessment including calcemia, parathormonemia, and albuminemia was requested at each control. We have thus distinguished the favorable evolution or cure, persistent and recurrent hyperparathyroidism. The patient was considered cured if, at 6 months, the corrected calcium level was normal. In normocalcemic forms of PHPT, the patient was considered cured if, at 6 months after parathyroidectomy, corrected calcemia and parathormonemia were normal. *Persistent hyperparathyroidism* was defined by the presence of hypercalcemia and/or hyperparathormonemia within 6 months of the initial parathyroidectomy. *Recurrence* was defined as hypercalcemia that recurs longer than 6 months after normocalcemia. Normal reference ranges were as follows: serum PTH, 15–65 pg/mL; calcium, 2.15–2.55 mmol/L; phosphate, 0.85–1.6 mmol/L; alkaline phosphatase, 98–279 IU/L; and vitamin D, >20 ng/mL.

Statistical analysis was performed with Epi info 3.3.2, Excel 2010, and SPSS 17 software. For the qualitative variables, results were expressed in simple frequencies and relative frequencies (percentages). Statistical analysis was carried out by χ^2 test for the comparison of percentages. Quantitative variables were presented as means ± standard derivation, medians, and minimum and maximum values (min–max). The comparison of averages was carried out by the Student's test.

This research received approval for conduct from the Badji Mokhtar Annaba University Ethics and Deontology Committee of the Faculty of Medical Sciences.

Table 1
Clinical characteristics of patients with primary hyperparathyroidism

Symptoms	*N* = 58	
	Number	Percentage
Bone manifestations	47	81
Pain	47	81
Fractures	18	31
Digestive manifestations	25	43.1
Abdominal pain	19	32.8
Nausea	14	24.1
Vomiting	8	13.8
Constipation	12	20.7
Peptic ulcer	3	5.2
Pancreatitis	1	1.7
Cardiovascular manifestations	27	48.2
High blood pressure	17	29.3
Palpitations	8	13.8
Precordialgia	2	3.4
Rhythm disturbances	3	5.2
Mitral breath	1	1.7
Tachycardia	2	3.4
Lipothymia	2	3.4
Neuromuscular manifestations	53	94.6
Asthenia	50	86.2
Weakness	38	65.5
Myopathy	10	17.2
Gait disturbances	16	27.6
Hypotonia	3	5.2
Amyotrophy	1	1.7
Renal manifestations	38	65.5
Stones	31	53.4
Bilateral	17	29.3
Unilateral	14	24.1
Nephrocalcinosis	4	6.9
Bilateral	3	5.2
Unilateral	1	1.7
Psychic manifestations	33	56.9
Memory disorders	20	34.5
Concentration problems	13	22.4
Melancholy	10	17.2
Confusional state	2	3.4
Irritability	14	24.1
Hallucination	1	1.7

RESULTS

Study Population. Between January 2002 and December 2013, we performed 145 parathyroidectomies in our department. The average of parathyroid surgeries performed was 12 parathyroidectomies per year. Our study series included 62 patients operated on for PHPT with an average annual frequency of 5 cases per year. The female/male ratio was 8:1. The mean age was 47.7 ± 15 years with no significant difference between the two sexes ($P = .13$). The most affected age group was between 40 and 60 years old.

Clinical Data. In order of frequency, the signs that prompted PHPT patients' consultation were bone symptoms in 42% of cases and renal symptoms in 37% of cases. In 7% of cases, the discovery was fortuitous. The mean duration of symptoms before diagnosis was 37.21 ± 53.4 months (range 2–168 months, median 24 months). At the time of surgery, more than a third of patients had been symptomatic for more than 2 years. Table 1 summarizes the different clinical signs noted in these patients.

Biochemical Features. Preoperative parathyroid hormone assays were markedly elevated in all patients. A PTH level greater than 400 pg/ mL was observed in 50% of cases with a mean of 867.78 ± 954.50 pmol/L. Hypercalcemia was detected in 75.8% of patients. It was greater than 2.86 mmol/L in half of them. The mean Ca was 2.95 ± 0.62 mmol/L. The mean values for serum phosphate and alkaline phosphatase were 0.78 ± 0.22 mmol/L and 880.52 ± 1432 IU/L, respectively. The vitamin D assay revealed a mean value of 17.42 ± 17.36 ng/mL.

Radiological Findings. The main radiological manifestations found were represented by subperiosteal resorption (65.5%), salt and pepper degranulation of the skull (58.6%), distal erosion of the clavicles (36.2%), and bone cysts and brown tumors (55, 2%). The BMD study, considering the T-score of lumbar spine, showed osteoporosis in 57.2% of cases and osteopenia in 25% of cases. These figures were 42.8% and 14.4% respectively, when the T-score of the whole body was used as a reference and 14.4% and 25% compared to the T-score of the hip. The mean T-score was −2.3 ± 1.6 SD at the lumbar spine and −1.1 ± 2.2SD at the hip.

Cervical ultrasound performed in 96.8% of patients was positive in 73.3% of cases. It was in favor of a monoglandular disease in 71.7% of cases. In 24 US examinations (55.8%), the thyroid gland was nodular. The overall sensitivity of US imaging was 60.7%. In patients free from nodular thyroid disease, it was 77.1%. When the thyroid was pathological, sensitivity dropped to 59.6%.

MIBI was performed in 48 patients (74.4%). It was positive in 93.7% of cases and found a monoglandular involvement in 85.4% of cases. The overall sensitivity of scintigraphy was 66.5%. In patients free from nodular thyroid disease, the sensitivity was 71%. When the thyroid was pathological, it dropped to 61.2%. The sensitivity of US-MIBI association was 100%.

Surgery. Thirty-four patients (54.8%) were operated on the conventional mode by BNE and 28 (45.2%) on the minimally invasive mode by MIOP. In the MIOP group, 18 patients underwent targeted

Table 2
Results of surgery at 6 months

Evolution	Global	According to the technique				P
		BNE	MIOP			
			Targeted	Unilateral	Total	
Cure	56 (90.3%)	31 (91.2%)	15 (83.3%)	10 (100%)	25 (89.3%)	.05
Persistent PHPT	5 (8.1%)	2 (5.9%)	3 (16.7%)	0	3 (10.7%)	
Recurrent PHPT	1 (1.6%)	1 (2.9%)	0	0	0	
Total	62	34 (100%)	18 (100%)	10 (100%)	28 (100%)	

parathyroidectomy and 10 had unilateral exploration. Thyroidectomy was associated with parathyroidectomy in 22 patients (35.5%).

Sixty-seven pathological glands were excised. Multiple gland disease was observed in 6.4% of patients. There was a predominance of lesions on the right (33 on the right and 27 on the left) with a predominance of lesions in the lower parathyroids. The average volume of the resected glands was 4.9 ± 6.2 cm^3 (range 0.26–34.01 cm^3), whereas their average weight was 5.6 ± 7.1 g (range 0.45–38.15 g).

Postoperative complications were dominated by hypocalcaemia and hungry bone syndrome (HBS). Hypocalcaemia was observed in 59.7% (37/62); it was severe (cCa < 1.9 mmol/L) in 41.9% (26/62), transient in 36 cases, and permanent in 1 case. HBS was noted in 19.3% of patients (12/62). These patients required high doses of intravenous calcium supplementation. After discharge from the hospital, the supplementation was adjusted during control visits to the endocrinologist depending on the laboratory values evaluated at that time.

Histopathological results showed an adenoma in 50 cases (80.6%), hyperplasia in 11 cases (17.8%), and a parathyroid carcinoma in 1 case (1.6%). The most common thyroid pathology in patients with concomitant thyroidectomy was multinodular goiter in 16 cases (72.8%). Three cases (13.6%) of thyroiditis and 3 cases of papillary thyroid carcinoma were noted.

Follow-Up Period. According to healing criteria set out in the methods section, global cure rate was 90.3%. It was similar between BNE and MIOP (*P* not significant) (Table 2).

DISCUSSION

PHPT risk is studied according to age and sex; prevalence is high in adults aged 40 to 70 years; it is 2 to 3 times greater in women. Postmenopausal women seem particularly affected [4]. In the United States, the prevalence has been estimated at approximately 2/1,000 inhabitants for women and 0.5/1,000 inhabitants for men [5]. In Europe, the prevalence of PHPT based on epidemiological studies is 21/1,000 in women between 55 and 75 years of age, which is the equivalent of about 3/1,000 in the general population [6].

The average annual frequency of the disease in our department was low (5 cases/year). The same observation was reported in the series of developing countries as shown in Table 3.

The sex ratio of our cohort is comparable to that recorded in developing countries [11,12]; however, it remains high compared to emerging and developed countries where the sex ratio varies from 1:2 to 1:3 [11]. The female prevalence of the disease has not been clearly elucidated to date. The drop in estrogen levels in women going through menopause has been associated with the prevalence of the disease at this time of life. PHPT is observed at any age from infancy to old age. However, the incidence of the disease gradually increases in adulthood. The average age at the time of diagnosis in developed and emerging countries is between the fifth and the sixth decade. In developing countries, the peak incidence is reported at 1 or 2 decades below [7,9,11,13]. The mean age at presentation in our cohort is close to that observed in Saudi Arabia and Iran [7,14], but it remains well above mean ages recorded in India and Pakistan [9,11]. Two elements can explain this gap between developed and developing countries: the first is that the statistics reported by developed countries include asymptomatic forms of the disease, whereas in developing countries, it is mainly symptomatic forms. The second element is the nutritional deficiency of vitamin D observed in this region of the world and which is responsible for the declaration of the disease at an early age [13]. If we look at the vitamin status of our patients, we find that among 18 patients in whom the vitamin D test was carried out, 14 had a deficit, which goes in the same direction of this hypothesis. The disease history of all our cases was long. Such long periods of evolution once again testify to the diagnostic delay of this pathology in our region.

In our series, bone manifestations were the most common presenting symptoms. This presentation of the disease contrasts with that observed in developed countries where osteitis became very rare after 1960. In developing countries, this form of the disease still exists. Prasarttong-Osoth [15] found in his series of 45 patients that 66.7% had bone signs; among them, 20% had fractures. A total of 45.7% had osteoarticular pain for Malabu [7], 25% had fractures for Afzal [13], and 93.5% had bone syndrome for Bahrami [14].

The incidence of fracture risk in PHPT is unclear. By comparing 1,201 patients with 3,601 controls in the Danish population, Vestergaard finds an increased risk of fracture before the diagnosis of PHPT [16]. The only risk factor found was age. The concentration of calcium does not influence the risk of fractures [17].

The high prevalence of hypercalcemia and elevated serum PTH levels in our study are compatible with many other Eastern studies [9,11] and contrast with results shown in Western series. This difference in the biochemical profile of the disease between developed and developing countries is due to the pronounced diagnostic delay in the latter.

In our series, the bone involvement in patients with PHPT resembles the one described by Albright and Reifenstein just over 60 years ago. Signs of demineralization were present in more than half of the patients. Osteitis fibrosacystica manifested by brown tumors on radiographs was observed in 55.2% of cases and fractures in 31% of cases. This finding is

Table 3
Frequency of annual recruitment in a few series in the literature

Author	Country	Department	Duration of the study	Number of patients	Frequency (case/year)
Malabu [9]	Saudi Arabia	Internal medicine	2000–2006	46	8
Paruk [10]	South Africa	Endocrine diseases	2003–2009	28	5
Bhansali [11]	India	General surgery	1993–2005	52	4
Bahrami [12]	Iran	Endocrine diseases	1985–2002	62	3
Our study	Algeria	ENT	2002–2013	62	5

very similar to the experiences of other developing countries. Bahrami [14] found signs of demineralization in 77.5% of patients with PHPT and bone fractures in 51.6% of cases. In a description of a series of 20 PHPT patients in India, bone disease was the most common mode of presentation, with 40% of pathological fractures and radiological signs of osteitis fibrosacystica in the vast majority of cases [13]. Low plasma concentrations of 25-OHD3 have been associated with the severity of skeletal manifestations of PHPT. Additional pathogenic factors can also contribute to the genesis and maintenance of these disorders.

BMD is the best examination to assess the bone impact of PHPT on demineralization of the skeleton. Minisola [18] studied several forms of hyperparathyroidism (asymptomatic and renal and radiological bone complications) and showed that only patients with bone complications have reduced spinal BMD. The BMD is lowered in the lumbar spine in the same proportions as in the hip. The study of densitometric data in developed countries revealed a heterogeneity of the studied groups (men and women, women with different menopausal status, and forms of hyperparathyroidism of varying severity) as well as measurement parameters. In developing countries, there are very few studies examining the impact of PHPT on bone status. Paruk [8] found a predominance of osteoporosis in the distal radius compared to the spine and hip (50%, 41%, and 18%, respectively), and Malabu [7] noted osteopenia–osteoporosis in 83% of patients.

The mean weight of the resected glands in our study was 5.6 ± 7.1 g (range 0.45–38.15 g). Compared to the various studies, this average is very high. In our experience, the heaviest adenomas were associated with severe forms of hyperparathyroidism. Several studies have attempted to assess the relationship between the weight of adenomas and preoperative and postoperative biological parameters. Bindlish et al [19] observed a statistically significant correlation ($P = .001$) between preoperative calcemia and parathormonemia and the weight of the adenoma in a series of 63 solitary adenomas.

The postoperative period was dominated by hypocalcemia which was severe in 41.9% of the cases. In all patients, it required intravenous calcium treatment during the first postoperative days, with an oral relay thereafter. Many authors have reported similar rates of postoperative hypocalcemia, such as Paruk [8] in 57.9% and Chan [20] in 20%–40%. All these series are from developing countries like Algeria where the disease profile has not changed significantly for decades, with persistent bone forms associated with vitamin D deficiency. Another form of severe hypocalcemia is hungry bone syndrome. This complication was observed in our series in 19.4% of cases. It is a direct consequence of the pathological state of the skeleton during PHPT. Various risk factors have been suggested for the development of HBS, including old age, weight/volume of the resected parathyroid glands, radiological evidence of bone disease, and vitamin D deficiency [21]. HBS is reported in 25%–90% of patients with radiological signs of fibrocystic osteitis versus only 0%–6% of patients without skeletal involvement [21].

Adenoma was the most common histological type in our series, which is similar to the literature results. We found 4 adenomas with oxyphil cells and 1 adenoma with clear cells. Oxyphil cell adenomas have long been considered nonfunctional. Recently, studies have shown a certain degree of activity of the oxyphil cells and consequently have proved that these adenomas can well be secreting [22]. Clear cell adenomas are very rare entities with a difficult histological diagnosis [23].

In our study, the overall success rate of parathyroidectomy in treating PHPT was 90.3%. Cure rates differ considerably in the literature. There are not many studies reporting the success rate of PHPT surgical treatment regardless of the technique used. Nevertheless, in a series of 1888 patients operated on for PHPT between 1965 and 2001 by both bilateral neck exploration and unilateral approach, Arnalsteen et al [24] published a cure rate of 97.6%. In general, the success rates usually reported after initial neck exploration, whether bilateral or unilateral, vary around 95% [24]. Failure rates, for their part, vary between 1% and 10% depending on the authors [25]. At first glance, we could conclude that our results fall at the lower limit of these standards. However, when examining the cases of failure (6 cases), we notice that it was a multiglandular lesion in 50% of cases and a recurrence in 16.7% of cases. Recurrent PPH is not seen in all studies as failure but rather as a late event in long-term development. As a result, failure rates are also very heterogeneous from one study to another, thus explaining the heterogeneity of cure rates.

In conclusion, the diagnosis of PHPT in our country is late. Management is often performed **after the appearance of bone and renal complications**. Compared to developed countries, PHPT is observed in younger subjects; this is likely due to a higher prevalence of vitamin D deficiency. Surgery is an effective way to reduce the secretion of parathyroid hormone. It improves the clinical symptomatology and the patients' quality of life. Systematic dosing of calcemia should help improve the diagnosis.

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Author Contribution

Souad Nouikes Zitouni conducted the study, wrote the article, and edited the manuscript according to the comments from the reviewers.

Conflict of Interest

The author declares no competing interest.

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