Frequency and Causes of Primary and Secondary Hyperparathyroidism in Patients Treated with Surgery at the University Clinical Hospital Mostar

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Abstract. Background. The aim of this study was to investigate the causes of hyperparathyroidism and whether there is a difference between the sexes. An additional goal was to determine the incidence of primary and secondary hyperparathyroidism and the most common surgical method of treatment.

Subjects and methods: 56 subjects were included in the study, of which 49 were women and 7 were men with diagnosed hyperparathyroidism. Subjects were patients who were treated endocrinologically and had elevated serum PTH (>7 pmol/L) as well as elevated Ca values (>2.6 mmol/L). The parameters considered are: age, sex, primary or secondary hyperparathyroidism, the most common surgical method of treatment.

The results: The study included 56 respondents, of whom 49 women and 7 men. All respondents had a diagnosis of hyperparathyroidism. Statistically, a significantly higher proportion of female sex than men with primary hyperparathyroidism was diagnosed ($\chi^2 = 8.64$; s.s = 1; $P = 0.003$). The youngest patient was 40 years old and the oldest 92 years. The average age was 63 years.

Most of the subjects in our study who had hyperparathyroidism also had parathyroid adenoma ($\chi^2 = 6.74$; s.s. = 1; $P = 0{,}009$).

The most common surgical procedure was partial parathyroidectomy, with almost the same ratio between women and men. There were no differences in surgical procedures with respect to sex ($\chi^2 = 1.25$; s.s. = 1; $P = 0.262$).

Parathyroidectomy of the lower and upper left as well as the lower and upper right parathyroid glands was equally common in our study (Table 4).

Conclusion. The incidence of primary hyperparathyroidism was higher than secondary. Primary occured more frequently in females while secondary hyperparathyroidism occured equally in both sexes. The most common cause of primary hyperparathyroidism was parathyroid adenoma, and secondary chronic renal failure. The most common surgical procedure was partial parathyroidectomy. Parathyroidectomy of the lower and upper left as well as the lower and upper right parathyroid glands was equally common.

Keywords: Primary hyperparathyroidism · Secondary hyperparathyroidism · Adenoma · Chronic renal insufficiency · Parathyroidectomy

A. Badnjevic and L. Gurbeta Pokvić (Eds.): CMBEBIH 2021, IFMBE Proceedings 84, pp. 609–616, 2021.
https://doi.org/10.1007/978-3-030-73909-6_71

1 Introduction

During the fifth week of gestation, the lower parathyroid glands develop from the third and the upper from the fourth gill arch. Fetal parathyroid glands are functional, respond to blood calcium levels, and produce parathyroid hormone. Most people have 4 glands, while 2–5% have 5 parathyroid glands and more [1, 2].

The parathyroid glands respond to low serum calcium levels by releasing PTH which increases serum calcium levels by acting directly on the bones and kidneys, also stimulates osteoclasts to resorb bone and mobilizes calcium into the blood. In the kidneys, PTH acts to reduce calcium clearance and stimulates the synthesis of 1, 25-dihydroxy vitamin D, which stimulates calcium absorption in the gastrointestinal tract [3].

The most common disorder of the parathyroid gland is hyperparathyroidism, we distinguish primary, secondary and tertiary. Primary and tertiary are treated surgically, and secondary is usually treated with medication [2].

Primary hyperparathyroidism is the third most common endocrine disorder, occurring more frequently in women than in men in all age groups [4, 5]. Occurrence in pregnant women is rare, and since neonatal mortality is associated with maternal hyperparathyroidism, early diagnosis is essential. Treatment should be individualized and includes conservative treatment, parathyroidectomy in the second trimester, or in the early postpartum period [6].

Primary hyperparathyroidism occurs due to a primary defect in the parathyroid glands, so that elevated serum calcium does not inhibit PTH release. Primary hyperparathyroidism is caused by solitary parathyroid adenoma in 80% of cases, 4 gland hyperplasia in 10–15% of cases, multiple adenomas in 5% of cases, and parathyroid carcinoma in less than 1% of cases [7].

In addition to generalized fatigue and weakness, primary hyperparathyroidism may present with symptoms such as vomiting, abdominal pain, constipation, peptic ulcer, and pancreatitis. Hyperparathyroidism may be the most significant manifestation of endocrine diseases in patients with MEN-I syndrome. Symptoms by the renal system are manifested by polyuria, polydipsia, nephrolithiasis. Bone disease can manifest as bone pain and pathological fractures. Neuromuscular syndrome improves after parathyroidectomy in 80–90% of patients. Many of the psychiatric symptoms improved after parathyroidectomy. Cardiovascular symptoms may include hypertension and cardiac arrhythmias. Hypertension can occur in 50% of patients [2, 8].

Biochemical characteristics include elevated serum calcium levels with elevated or inappropriately normal PTH levels [9].

Surgery is the only definitive cure for primary hyperparathyroidism, avoiding long-term complications. Parathyroidectomy is indicated for symptomatic treatment or persistently elevated serum calcium. In some patients, existing comorbidities may prevent the need for surgery [3, 10].

Secondary hyperparathyroidism is most commonly caused by chronic renal failure. It is characterized by high serum PTH, glandular hyperplasia, and disbalance of mineral metabolism [11, 12].

These damaging effects may contribute to an increased risk of cardiovascular morbidity and mortality in patients with end-stage renal disease [13]. Calcium and phosphorus

homeostasis is maintained through a complex connection between bones, intestines, kidneys, and parathyroid glands. PTH is probably the most important regulator of calcium metabolism [14].

In patients with damaged renal function, who are on dialysis, physiological control of mineral balance via parathyroid hormone through the kidney fails and hyperparathyroidism progresses. Ca-sensory receptor and vitamin D receptor abnormalities are associated with the pathogenesis of secondary hyperparathyroidism [15]. Abnormalities in renal tubular phosphate absorption lead to decreased phosphate excretion and hyperphosphatemia. Damage of renal conversion of 25-hydroxycolicalcaliferol to 1,25-dihydroxycholecalciferol also causes a decrease in intestinal calcium absorption. In combination, elevated serum phosphate levels and decreased vitamin D production result in decreased serum calcium levels and hypocalcemia. Stimulation of the parathyroid glands by chronic hypocalcemia results in hyperplasia of all glands [11, 12].

Early diagnosis of secondary hyperparathyroidism in chronic renal patients is crucial [16]. Treatment is medicamentous [2].

Parathyroidectomy may be useful for certain patients with severe secondary hyperparathyroidism and clinical symptoms [17].

Tertiary hyperparathyroidism occurs when the cause of stimulation is corrected, but the glands remain autonomically hyperfunctional [2]. It usually occurs in patients with chronic kidney disease after kidney transplantation, which is a therapeutic procedure in secondary hyperparathyroidism [18].

Unlike secondary, tertiary hyperparathyroidism often requires total parathyroidectomy [19].

2 Subjects and Methodes

Cohort form of research. The study included 56 subjects, 49 subjects were women and 7 subjects were men with diagnosed hyperparathyroidism hospitalized at the Clinic of Otorhinolaryngology and Maxillofacial Surgery and underwent surgery, partial or total parathyroidectomy at the University Clinical Hospital (SKB) Mostar in the period from January 1st 2009 to February 22nd 2019. Subjects were endocrinologically treated patients with elevated serum PTH (>7 pmol/L) and Ca (>2.6 mmol/L). Serum PTH and Ca values were obtained by taking serum samples from patients. The concentration of ionized calcium in serum was determined by ion selective electrode (ISE) potentiometry on a Rapidpoint400 analyzer manufactured by Siemens. PTH was determined on a Cobas e 411 automated analyzer (Roche Diagnoatics GmbH, Mannheim, Germany) by the ECLIA method (Electrochemiluminescence immunoassay electrostimulation method). Patient data were collected from the Hospital Information System (BIS) based on medical records in the form of a medical history. The parameters considered are: age, sex, primary or secondary hyperparathyroidism, the most common surgical method of treatment.

For statistical analysis of the obtained data was used the software systems SPSS for Windows (version 13.0, SPSS Incorporated Chicago, Illinois, USA) and Microsoft Excel (version Office 2010, Microsoft Corporation, Redmond, Washington, USA). The χ^2 test was used to test the significance of the observed differences. The limit of statistical significance was set at $P < 0.05$. P values that could not be expressed to three decimal places are expressed as $P < 0.001$.

3 Results

The study included 56 subjects, 49 subjects were women and 7 subjects were men with diagnosed hyperparathyroidism. The youngest patient was 40 years old and the oldest 92 years old. The average life expectancy was 63 years. There was a statistically significantly higher proportion of females compared to males with a diagnosis of primary hyperparathyroidism ($\chi^2 = 8.64$; s.s = 1; $P = 0.003$) (Table 1).

Table 1. Distribution of patients with primary and secondary hyperparathyroidism by gender.

	Primary hyperparathyroidism		Secondary hyperparathyroidism			
	Number of patiens	%	Number of patiens	%	P	χ^2
Male	4	8,0	3	50,0	0,003	8,64
Female	46	92,0	3	50,0		

Most of the subjects in our study who had hyperparathyroidism also had parathyroid adenoma ($\chi^2 = 6.74$; s.s. = 1; $P = 0{,}009$) (Table 2).

Table 2. Distribution of patients according to the etiology of hyperparathyroidism.

	Adenoma		Chronic renal failure			
	Number of patiens	%	Number of patiens	%	p	$\chi 2$
Male	4	8,16	3	42,86	0,009	6,74
Female	45	91,84	4	57,14		

The most common surgical procedure was partial parathyroidectomy, with almost the same ratio between women and men. There were no differences in surgical procedures with respect to sex ($\chi^2 = 1.25$; s.s. = 1; $P = 0.262$) (Table 3). Parathyroidectomy of the lower and upper left as well as the lower and upper right parathyroid glands was equally common in our study (Table 4).

Table 3. Frequency of partial and total parathyroidectomy

	Partial parathyroidectomy		Total parathyroidectomy			
	Number of patiens	%	Number of patiens	%	P	χ^2
Male	7	12,96	0	00,0	0,262	1,25
Female	47	87,04	2	100,0		

Table 4. Frequency of parathyroidectomy of individual glands.

Parathyroidectomy	Number of patiens	%	P	χ^2
Right lower parathyroid gland	9	16,07 (0.36)		
Right lower and upper parathyroid gland	19	33,92 (1.07)		
Left lower parathyroid gland	8	14,28 (0.82)	0,23406	5.565
Left lower and upper parathyroid gland	19	33,92 (1.07)		
Right and left lower parathyroid gland	1	1,78 (2.25)		

4 Discussion

In their study, Castellano et al. [20] found that the biochemical activity of primary hyperparathyroidism is gender independent, but the clinical picture is different, mainly due to the menopausal condition. Shah and coworkers [21] state that age and gender have a significant impact on the presentation of primary hyperparathyroidism. Bone pain and rickets were more common in children and adolescents, while kidney stones were more common in adults.

Bandeira et al. [22] claim that vitamin D deficiency or complete deficiency in primary hyperparathyroidism may contribute to the severity of the disease itself. Carsote et al. [23] also found that careful monitoring of 25-hydroxy vitamin D is crucial for a good outcome of parathyroidoidectomy.

In their study, Sharma et al. [24] state that one in every 20 patients with urolithiasis had primary hyperparathyroidism.

The data obtained in our study agree with the data provided by Jiang et al. [25] in their study. A larger number of patients had (72%) parathyroid adenoma as the cause of primary hyperparathyroidism, and in 9.3% of cases was parathyroid carcinoma. The incidence of parathyroid cancer was higher in men.

La et al. [26] conducted a study on the quality of sleep of patients who underwent parathyroidectomy for primary hyperparathyroidism and thyroidectomy for thyroid disease. Preoperatively, patients with primary hyperparathyroidism had poorer sleep quality, and after the procedure, their sleep quality improved, and there were no changes in patients with thyroid disease. In their study, Ma et al. [27] suggest that parathyroidectomy may beneficially modify calcium and phosphorus metabolism and bone mineral density in patients with secondary hyperparathyroidism undergoing hemodialysis. The question is when to perform parathyroidectomy in patients who are waiting for a kidney transplant and suffer from secondary hyperparathyroidism. Littbarski et al. [28] state that parathyroidectomy should be performed before transplantation, and if the procedure cannot be performed then as early as the first year after transplantation if possible. Also Parikh et al. [29] state that parathyroidectomy can lead to transient dysfunction of allogeneic kidney transplantation with possible recovery of graft function up to 12 months after parathyroidectomy.

Chudzinski and colleagues [30] in their study state that parathyroidectomy did not significantly impair renal transplant function, but there were transient decreased functions in the early postoperative period.

Konturek et al. [31] in their study state that partial parathyroidectomy is also a safe and effective treatment option for secondary hyperparathyroidism.

It remains unclear whether partial or total parathyroidectomy gives better results for secondary hyperparathyroidism. Isaksson et al. [32] investigated mortality, cardiovascular disorders, hip fractures, and the need for re-parathyroidectomy in patients on renal replacement therapy. They considered age, sex, cause of kidney disease, pre-existing cardiovascular disease, time on dialysis, kidney transplantation as well as medical treatment before parathyroidectomy. The study concludes that there is a higher cardiovascular risk after total parathyroidism than after partial. Filho et al. [33] state that parathyroidectomy increases the quality of life expectancy of hemodialysis patients with secondary hyperparathyroidism regardless of the type of procedure.

5 Conclusions

In this paper, we investigated the causes of hyperparathyroidism, and whether there is a difference between the sexes. We wanted to determine the frequency of primary and secondary hyperparathyroidism, and the most common surgical method of treatment. The study included 56 patients diagnosed with hyperparathyroidism. The average life expectancy was 63 years. There was a significantly higher proportion of females (92%) compared to males (8%) in patients with primary hyperparathyroidism, while in secondary hyperparathyroidism the number of patients was equal to both males and females. Research has shown that adenoma was the most common cause of hyperparathyroidism. The most common surgical procedure was partial parathyroidectomy. The study showed that parathyroidectomy of the lower and upper left as well as the lower and upper right parathyroid gland was equally common.

In our study, partial parathyroidectomy was performed in 87.04% of women and 12.96% of men, while total was performed only in women.

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