

Surgical Contribution to the Management of Primary Hyperparathyroidism

Libánský P.¹, Adámek S.¹, Broulík P.², Pafko P.¹, Pozniak J.¹, Tvrdoň J.

¹Third Department of Surgery of the First Faculty of Medicine and Teaching Hospital Motol, Czech Republic;

²Third department of Medicine of the First Faculty of Medicine, Charles University in Prague and General Teaching Hospital in Prague, Czech Republic

Received June 30, 2004, Accepted September 9, 2004

Abstract: Surgical management of primary hyperparathyroidism is a very effective method. The target is to cure primary hyperparathyroidism and to reach normal calcium levels. This results in an improvement of health condition and resolution or at least moderation of symptoms. Complications are infrequent and mortality is very low. Surgical management is definite, safe and effective. Authors of this article address the diagnosis of primary hyperparathyroidism, clarify bone, metabolic and biochemical syndromes and present series of 151 patients that have been operated on at the 3rd Department of Surgery of the Motol University Hospital, Prague, with the diagnosis of primary hyperparathyroidism. The survey is focused on the primary hyperparathyroidism concomitant diseases and on the possible sequelae in the postoperative period.

Key Words: Primary hyperparathyroidism – Bone syndrome - Metabolic syndrome – Biochemical syndrome – Surgical treatment

Mailing address: Petr Libánský, MD., Ke Karlovu 8, 120 00 Praha 2,
Phone: +420 224 438 030, e-mail: libanskyp.III.chir.kl.FNM@seznam.cz

Introduction

Primary hyperparathyroidism is independent hyperfunction of one or more parathyroid glands that results in increased parathormone levels, which influences the serum calcium and phosphate levels. Disorder of calcium, phosphate and bone metabolism frequently results in biochemical, renal and bone syndromes. In case the hyperparathyroidism is a compensatory process to diseases associated with calcium loss, it is called the secondary one, and it is usually associated with hyperplasia of parathyroid glands. Tertiary hyperparathyroidism develops from secondary hyperparathyroidism, in cases when the secretion becomes autonomous, e.g. it continues even after the normalisation of calcium blood levels as it is in case of kidney transplant.

The underlying cause of primary hyperparathyroidism is most frequently a single or multiple adenoma, hyperplasia and rarely a cancer. The aetiology is unknown but discussion is addressing the molecular defect of PTH gene, and also the effect of irradiation in the parathyroid glands region [6]. Familiar hyperparathyroidism occurs rarely, it may develop independently, but usually is a part of MEN syndromes – multiple endocrine neoplasia [8].

Primary hyperparathyroidism is the third most prevalent endocrinological disorder. Primary hyperparathyroidism may occur at any age, it is rare in children, and is more frequent in women during menopause period. In the Czech Republic, the prevalence is 1 case of primary hyperparathyroidism per 100 000 inhabitants. Primary hyperparathyroidism is often subclinical or asymptomatic.

Bone, metabolic and biochemical syndrome

Clinical manifestations of primary hyperparathyroidism are the most distinct in two areas: the bone and kidney. In case of kidney, manifestations usually include kidney stones, nephrocalcinosis, polyuria, polydipsia, urinary tract infection and impaired concentration capacity of the kidney. Kidney stones may cause obstruction and infection of the diseased kidney with gradual reduction of renal functions and subsequent renal failure. The symptoms of kidney disease are sometimes called the renal syndrome.

Bones can be affected in various ways. Excess of parathormone has an aggressive effect on the bone. It dissolves the bone mineral, stimulates osteoclasts and fibrose bone remodelling, which can result in cysts and large brown tumour development. Clinical manifestations include bone ache, especially in the back, hips and lower extremities. In advanced disease, deformities or fractures may be detected. X-ray yields finding of subperiosteal resorption, most frequently in the radial or ulnar surface of the distal digital bones [6]. The symptoms affecting bones are sometimes called the bone syndrome.

Patients with primary hyperparathyroidism have higher incidence of peptic ulcer, pancreatitis and gall bladder stones. These patients often have various mental disorders, beginning with feeling of muscle weakness up to neuropsychiatric

dysfunctions that are often attributed to ageing. Hypercalcemia also influences the heart and circulation; patients with pHPT have increased prevalence rate of arterial hypertension. Hypercalcemia with levels reaching 4 mmol/l may result in chemical cardiac arrest in the systole.

Diagnosis of primary hyperparathyroidism is based upon hypercalcemia, hypophosphatemia and elevated serum parathormone level. These patients have also increased urinary calcium loss and increased urinary phosphate loss, increased alkaline phosphatase activity, especially its bone isoenzyme. The verification is based upon calculated urinary phosphate clearance that is increased. The sum of such abnormal findings is sometimes called the biochemical syndrome.

Differential diagnosis is broad due to unspecific and variable clinical presentation and hence, close co-operation between the experienced endocrinologist and the surgeon is of critical importance. In this context I would like to acknowledge all endocrinologists that have entrusted their patients into our hands.

In case of unequivocal diagnosis of primary hyperparathyroidism, surgical treatment is indicated to remove the cause of the disease [2]. Surgical therapy is definite, safe and effective.

In elective surgery on parathyroid glands it is desirable to attempt presurgical localisation of the affected parathyroid gland, however, reliability of localisation investigations is less than reliability of perioperative detection. The most common and accessible investigations include ultrasonography, followed by MIBI scan, CT scan and MRI, recently also PET/CT. These investigations, especially ultrasonography, may show not only localisation of the pathological parathyroid gland but also any pathology of the thyroid gland. Among invasive methods

Table 1 – The collection of patients and their average age

	Number	Average age
Men	36	54.50
Women	115	60.30
Total	151	58.92

Table 2 – Did the operation help your problems?

	Men	Women	Total	Percentage	Average age
Yes	31	99	130	86.09%	59.18
No	2	7	9	5.94%	50.22
No problems before the operation	2	4	6	3.96%	61.67
Help partial		5	5	3.3%	64.00
Died of the infarct	1		1	0.66%	62.00
Total	36	115	151		58.92

prevail selective arteriography and selective blood sampling of parathormone levels. However, neither of the localisation methods does not reach the success rate of a surgeon, since when combined they reach (ultrasonography + MIBI + MRI) 80 to 85% success rate, whereas an experienced surgeon has success rate over 95% [3].

It should be noted that a surgeon has to have knowledge not only of anatomy but also embryology.

Methods

From 1994 to 2003 we have operated 453 patients with diagnosis of primary hyperparathyroidism at the Third department of Surgery of the Charles University First Faculty of Medicine in Motol University Hospital, Prague. All patients had preoperative investigation, all of them were examined endocrinologically, usually at the Third department of Medicine of the Charles University First Faculty of Medicine, Prague, with established diagnosis of primary hyperparathyroidism. Surgeries were performed in the standard way; specialists at our department prefer bilateral exploration of the neck, which includes revision of all 4 parathyroid glands [1]. A drain is ordinary inserted, which is removed 1 to 2 days after the surgery and serum calcium level is monitored after surgery. Patients are discharged from the hospital usually the third day after the surgery. Patients are then followed up at referral endocrinology clinics. To determine the health

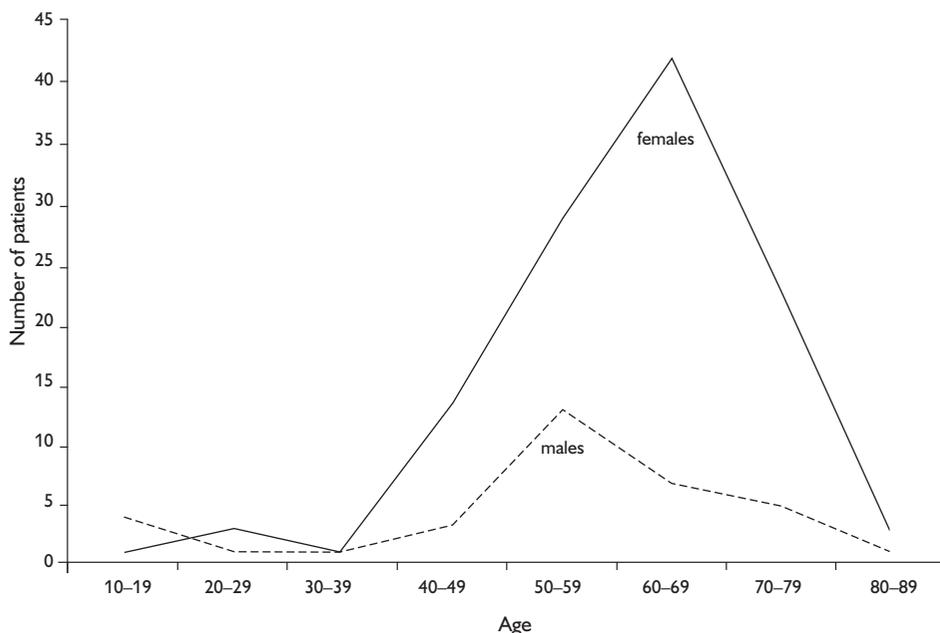


Fig. 1 – The number of patients according to the age and the sex

condition after the surgery, a questionnaire was prepared and sent to 203 patients. It includes all patients operated since January 1, 2001 till December 31, 2003 with diagnosis of primary hyperparathyroidism. The questionnaire was sent to our patients 4 months to 3 years after surgery. Out of 203 questioned persons we have received answers from 151, whereas 44 patients responded to only a part of the questionnaire. The questions were focused on the subjective assessment whether the surgery success, late postoperative complications, and hypocalcemia estimation result from hospitalisation or they are effects of other drugs. We have also monitored postoperative prevalence of symptoms or diseases that may be co-morbidity in patients with diagnosed primary hyperparathyroidism. The questionnaire's objective was to determine efficacy of the surgical treatment of primary hyperparathyroidism.

Results

The study population included 151 patients out of whom 115 were females and 36 males (ratio about 3:1). Mean age 59 years, the youngest patient was 10 years old and the oldest one 84 years. Out of 151 patients, 130 claimed resolution of symptoms that preceded the surgery, 6 patients had no symptoms before surgery, and partial resolution of symptoms was stated by 5 females, 9 patients were not satisfied with the treatment. 1 patient died 4 months after surgery due to myocardial infarction at the age of 62 years, which was unrelated with the performed surgical procedure. Complications with wound healing were fortunately rare, postoperative bleeding or haematoma was not detected in our population, wound complications occurred 4 times, in 2 cases the wound was healing by keloid, in 1 case an abscess was diagnosed and in 1 case seroma. Persisting hoarse voice based on laryngeal recurrent nerve paresis was claimed by 3 patients, which is 2.04%. 4 patients complained on persisting symptoms of paresthesia, 7 patients use after surgery tachystin to treat hypocalcemia, 34 patients use calcium in different forms, most frequently to enhance bone metabolism with unaltered levels of plasma calcium, and 109 patients use no drugs. Out of diseases that may be associated with primary hyperparathyroidism after surgery we have detected angina pectoris syndrome in 3 patients (2.04%), stroke developed in 2 patients (1.36%), fracture was diagnosed in 4 patients (2.72%), and renal colic in 3 patients (2.04%).

Table 3 – Complications of the wounds after the operation

Complications	Total
No	145
Absces	1
Keloid	3
Serom	1
Total	150

Table 4 – Have you been hospitalized for the hypocalcemia since the operation?

Hospitalization for the hypocalcemia?	Men	Women	Total	Percentage	Average age
No	34	112	146	97.33%	58.84
Yes	1	3	4	2.67%	61.25
Total	35	115	150		58.90

Table 5 – Have you had syndrom of angina pectoris since the operation?

Sy anginy pectoris?	Men	Women	Total	Percentage	Average age
No	21	83	104	98.11%	58.40
Yes	1	1	2	1.89%	68.00
Out of answers	13	31	44		59.66
Total	35	115	150		58.90

Table 6 – Have you had vascular cerebral epizode since the operation?

Epizode?	Men	Women	Total	Percentage	Average age
No	22	83	105	99.06%	58.56
Yes	1	1	2	0.94%	61.00
Out of answers	13	31	44		59.66
Total	35	115	150		58.90

Table 7 – Have you had any fracture since the operation?

Fracture?	Men	Women	Total	Percentage	Average age
No	21	82	103	97.17%	58.50
Yes	1	2	3	2.83%	61.67
Out of answers	13	31	44		59.66
Total	35	115	150		58.90

Table 8 – Have you had the renal colica since the operation?

Renal colica?	Men	Women	Total	Percentage	Average age
No	22	82	104	98.11%	58.75
Yes	1	2	3	1.89%	50.00
Out of answers	13	31	44		59.66
Total	35	115	150		58.90

Discussion

Predominance of female patients compared to males in 3:1 ratio corresponds to data reported in the literature (74%) [5]. Females presented with the disease significantly more frequently around the period of menopause, their average age (60.3 years) was also higher than in male population (54.5).

The treatment of choice in causal therapy of primary hyperparathyroidism is a removal of hyperfunctional parathyroid gland. The operation is considered successful to remove the symptoms by 86% of patients. The operation is considered unsuccessful in 6% of patients, out of these 9 patients 2 have persisting hypercalcemia, 4 patients have persisting arthralgia (which could be caused by another aetiology), 1 patient claims persisting mental problems, 1 patient claims persisting urinary problems and 1 patient reported diarrhoea. 3% of patients consider the operation to be partially successful, especially those patients who had postoperative complications such as hoarseness of voice or paresthesia.

Perioperative complications include especially unsuccessful detection of the affected gland with resulting persisting hypercalcemia, undetected multiple disease of parathyroid glands which may cause relapse even after several months. 2 patients had postoperative hypercalcemia, we also follow up with 1 patient in whom the surgery was postponed due to anaesthetist's indication and the surgery was not performed.

Removal of parathyroid adenoma or hyperplastic parathyroid glands is associated with decrease of serum calcium levels usually within 48 hours. Most affected are those patients with bone syndrome with long-standing deficit of calcium in bones. Characteristic symptoms include digital paresthesia, perioral itching, Chvostek's sign, and digital tremor or carpedal spasms. Untreated hypocalcemia may result in tetania with possible lethal effect [11]. Short-term hypofunction of parathyroid glands may be caused by ischemic damage due to surgical trauma. This short-term transient hypocalcemia is common. Less frequent is so called protracted hypocalcemia that is caused by remineralisation and it is sometimes called as a syndrome of hungry bone. This is caused by excessive uptake of calcium into the bone. In these patients it is recommended to supplement calcium in oral form. In our population there were 4 patients with postoperative paresthesia, 7 patients use tachystin to treat hypocalcemia. It is of interest that all of 7 patients who have to use tachystin due to hypocalcemia consider the surgery to be successful, 2 of them partially successful – these are patients with paresthesia.

Bleeding into the closed compartments of the neck is also serious complication because it may cause respiratory insufficiency. Signs of increasing pressure in the neck due to bleeding are an indication for immediate revision with wound reopening and pressure relief. We had not encountered this complication.

Also other wound complications were infrequent.

Out of other complications it is the damage of the laryngeal recurrent nerve with voice impairment that is very poorly tolerated by the patients. Some surgeons consider preparation of the laryngeal nerve as a routine, others do not consider the preparation of the laryngeal recurrent nerve in primary uncomplicated surgery to be necessary [11]. Our patients reported persistent paresis of the laryngeal recurrent nerve in 3 cases, which represents 2%. However, it must be noted that our population does not distinguish between primary and secondary surgeries, e.g. after the previous thyroid gland surgery, and procedures performed in connection with sternotomy were not evaluated.

Another point of interest is cardiovascular disease. This type of complication is the most frequent cause of death with both successfully treated and untreated primary hyperparathyroidism. It has been suggested that untreated primary hyperparathyroidism causes endothelial dysfunction, left ventricular hypertrophy, cardiac rhythm disturbances and arterial hypertension. We saw 1 death due to myocardial infarction in our population sample, literature states death due to cardiovascular disease in 53% during 12.3 years follow up, out of that 32% due to myocardial infarction [9].

Other complications include psychological problems comprising broad spectrum of various symptoms that are difficult to follow up and evaluate. Persisting psychological problems occurred in 3 patients in our study population. Since 1990 we have seen substantial reduction of time from first symptoms occurrence till diagnosis is established and the surgery is performed. We have seen substantial reduction of prevalence of severe hypercalcemia and especially severe bone finding. We believe that this is a result of good cooperation with general practitioners and others who test serum calcium and phosphate levels as screening.

The prognosis of renal recovery is determined by corresponding scope of kidney damage before surgical treatment of primary hyperparathyroidism. Literature states that approximately 80% of patients have no renal or bone symptoms [4, 7, 10]. These data are consistent with our findings.

Conclusion

Surgical management of primary hyperparathyroidism is a highly efficient method. The objective is to cure primary hyperparathyroidism and to reach normal calcium levels. This results in improvement of health condition and resolution or at least moderation of symptoms. Complications are not frequent and mortality is very low. Surgical treatment in hands of an experienced surgeon has 95% and higher success rate for permanent cure. Besides, this surgery has near-zero mortality and postoperative complications are rare. In hands of the experienced endocrinological surgeon, there are only few surgical interventions with such high success rate as this surgical treatment

of primary hyperparathyroidism. However, the diagnosis must be established reliably and then the success has to be also attributed to the indicating endocrinologist.

References

1. ADÁMEK S., LIBÁNSKÝ P., TVRDOŇ J., PAFKO P., BROULÍK P.: Personal experience with a bilateral approach in the surgical treatment of primary hyperparathyroidism. (A group of 222 patients with surgery for primary hyperparathyroidism from 1994 to 2000). *Rozhl. Chir.* 81: p. 443–9, 2002.
2. ADÁMEK S., VAVŘÍK J., SCHUTZNER J., BROULÍK P., BELŠÁN T.: Surgery for primary hyperparathyroidism in patients with concomitant nodular goiter, *Sb. Léč.* 101: p. 297–305, 2000.
3. ADÁMEK S., VAVŘÍK J., SCHUTZNER J., BROULÍK P., BELŠÁN T.: Importance and reliability of localization examinations in primary hyperparathyroidism., *Sb. Léč.* 101: p. 289–295, 2000.
4. BRITTON D. C., THOMPSON M. H., JOHNSTON I. D., FLEMING L. B.: Renal function following parathyroid surgery in primary hyperparathyroidism. *Lancet.* 10/2 (7715): p. 74–5, 1971.
5. ČERNÝ J. A KOLEKTIV: Špeciálna chirurgia, IV.díl, Osveta, Martin, 1995, p. 73–86
6. KLENER P. A KOLEKTIV: Vnitřní lékařství, IV.díl. Karolinum, Praha, 1997, p. 41–48
7. JUNGINGER T., PICHLMAYER H., ZENKER R.: Primary hyperparathyroidism. Diagnosis – surgery-results. *Langenbecks Arch. Chir.* 338/1: p. 27–41, 1975.
8. F - LORENZ K., DRALLE H.: Chirurgie des Hyperparathyreoidismus, *Der Chirurg* 74: p. 593–616, 2003.
9. ORLO H. CLARK, DUH Q. Y.: Textbook of Endocrine Surgery, W.B. Saunders Company, 1997, p. 277–439.
10. PURNELL D. C., SMITH L. H., SCHOLZ D. A., ELVEBACK L. R., ARNAUD C. D.: Primary hyperparathyroidism: a prospective vlinical study. *Am. J. Med.* 50: p. 670–8, 1971.
11. SCHWARZ A. E., PERTSEMILIDIS D., GAGNER M.: Endocrine Surgery Marcel Dekker Inc., New York, U.S.A., 2004, p. 213–305.