Recurrent Primary Hyperparathyroidism in Multiple Endocrine Neoplasia Type 1 Syndrome

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Summary

Primary hyperparathyroidism is a common endocrinopathy. Multiple Endocrine Neoplasia Type 1 (MEN1) is a rare autosomal dominantly inherited endocrine tumor predisposition syndrome, with one of main manifestations being primary hyperparathyroidism. We retrospectively evaluated a set of 1011 patients who underwent surgery for primary hyperparathyroidism between the years 2018–2022, and found 78 (8 %) patients who underwent reoperations and 27 patients with MEN1 syndrome. In the group of patients with MEN1 syndrome, 7 (35 %) needed reoperations. Patients with multiple endocrine neoplasia syndrome have a higher risk of needing reoperation. Genetic testing can help identify MEN1 syndrome preoperatively and to better evaluate the approach to surgery.

Key words

Primary hyperparathyroidism • Parathyroid adenoma • Parathyroidectomy • MEN1 syndrom

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Introduction

Primary hyperparathyroidism is a disease caused by the excessive secretion of parathyroid hormone from one, more or all parathyroid glands. After establishing a clear diagnosis of primary hyperparathyroidism, the success of therapy depends on the experience and judgment of the surgeon performing the operation to remove the hyperfunctional pathological parathyroid gland. The goal is to achieve normal calcium levels and definitively cure the primary hyperparathyroidism, and in doing so improve the health status of the patient improves and ameliorating or significantly decreasing his/her difficulties. This is not always achieved in the primary operation, however, and sometimes reoperations are necessary. Such reoperations can be divided into surgery for recurrent or persistent primary hyperparathyroidism. Recurrent primary hyperparathyroidism is a recurrence of the disease, i.e. a rise in calcium and parathyroid hormone levels not earlier than 6 months after surgery, after which normocalcemia had been achieved. Persistent primary hyperparathyroidism is a disease in which elevated levels of calcium and parathyroid hormone persist postoperatively.

One contributing factor in recurrent or persistent primary hyperparathyroidism is multiple endocrine neoplasia type 1 (MEN1) syndrome, a rare genetically determined disease that is characterized by a predisposition for the development of tumors of the parathyroid glands, hypophysis and neuroendocrine tumors of the pancreas or intestine.

Methods

This retrospective study included patients operated on in the 3rd Department of Surgery, 1st Faculty of Medicine, Charles University in Prague or the Motol University Hospital, Prague, for the diagnosis of primary hyperparathyroidism in the period from 1/1/2018 to 31/12/2022. MEN1 syndrome was defined on the basis of a genetic examination and a proven mutation. Patients who fulfilled the clinical criteria of MEN1 syndrome and with negative genetic testing were designated as having MEN1-like syndrome. In addition to primary hyperparathyroidism, in order to be included in the MEN1-like syndrome group it was also necessary that the patients manifested either an adenoma of the anterior part of the pituitary gland (prolactinoma, somatotropic or corticotropic adenoma, non-functional adenoma) or neuroendocrine tumors of the duodenum or pancreas.

In all patients, age, sex, preoperative total calcium level, preoperative intact parathyroid hormone level, postoperative total calcium level, and ectopic localization were evaluated. Multiple involvement of the parathyroid glands was considered as the presence of two or more enlarged parathyroid glands detected during operations.

Data are reported as means ± S.E.M. Statistically significant differences between groups (persistent vs. recurrent primary hyperparathyroidism) were analyzed with the Student´s T-test using MS Excel with $p<0.05$.

Results

We retrospectively evaluated a set of 1011 patients (average age 60 years) who underwent surgery at the 3rd Department of Surgery, 1st Faculty of Medicine, Charles University in Prague or the Motol University Hospital, Prague, between the years 2018–2022. In this group, we found 78 (8 %) patients who underwent a reoperation for recurrent (4 %) or persistent (4 %) primary hyperparathyroidism. Of the 78 patients who needed reoperations for primary hyperparathyroidism, 43 (56 %) had persistent primary hyperparathyroidism and 35 (44 %) had recurrent primary hyperparathyroidism (Table 1). No statistically significant differences were found between groups for any of the studied parameters (Table 1).

Table 1.

	Persistent pHPT	**Recurrent pHPT**	**Total**
Number of patients	43	35	78
Average age (years)	59.23 ± 2.14	57.31 ± 2.28	58.37 ± 1.56
Number of women	76.74 %	77.14 %	76.92 %
Mean level of total calcium before operations (mmol/l)	2,83 ± 0.05	2,78 ± 0.03	2.81 ± 0.03
Mean iPTH level before surgery (pmol/l)	18.61 ± 2.95	14.63 ± 1.81	16.88 ± 1.84
Mean level of total calcium 24 hours after surgery (mmol/l)	2.28 ± 0.03	2.34 ± 0.03	2.31 ± 0.02
Ectopic localization	15 (34.88 %)	8 (22.86 %)	23 (29.49 %)
Number of reoperations in patients with genetic confirmed MEN1 syndrome	2	5	7

Abbreviations: pHPT – primary hyperparathyroidism; iPTH – serum parathormone

Table 2.

	Total (MEN1 +MEN1 like)
Number of patients	27
Mean age (years)	38.70 ± 2.46
Number of women	62.96 %
Mean preoperative total calcium level (mmol/l)	2.88 ± 0.02
Mean preoperative iPTH level (pmol/l)	18.12 ± 3.74
Average level of total calcium 24 hours after surgery (mmol/l)	2.26 ± 0.04
Ectopic location	3 (11.11 %)

Table 3.

	Total (MEN1 +MEN1 like)	Subtotal PTx Focused performance Other performance	Subtotal PTx Focused performance Other performance	Subtotal PTx Focused performance Other performance
Number of patients	27	19	2	6
Transient hypoparathyroidism	18	14	1	3
Permanent hypoparathyroidism	4	3	0	1
Transitory paresis of recurrent laryngeal nerve	3	1	0	2
Permanent paresis of recurrent laryngeal nerve	1	1	0	0

Abbreviations: PTx - Parathyreoidectomy

In the group of 1011 patients, 27 patients with a genetic confirmation of MEN1 syndrome and 3 patients with MEN-like syndrome were found (Table 2).

Of the 27 patients with MEN1 or MEN1-like syndrome, 7 patients underwent reoperation: 5 of them for recurrent primary hyperparathyroidism and 2 of them for persistent primary hyperparathyroidism. Compared to patients with sporadic primary hyperparathyroidism, patients with the presence of MEN1 syndrome were younger (on average by 21 years). There were 10 men and 17 women in the group with MEN1 syndrome. Surgical approaches and complications in patients with MEN1 syndrome are summarized in Table 3.

At the time of surgery, 14 patients with MEN1 syndrome had the involvement of multiple endocrine organs: a pituitary tumor was described in 5 patients, a pancreas was involved in 11 patients, and an adrenal tumor was found in 2 patients.

Altogether 20 patients had a primary operation, and 7 (35 %) patients had a reoperation. Reoperations in these 7 patients were performed after an average interval of 71 months (20–143 months) from the previous operation.

Discussion

Surgery is currently the main treatment option for primary hyperparathyroidism. The number of cases that need reoperations for persistent or recurrent primary hyperparathyroidism range from 2.5 to 9.4 % [1,2]. In our group, reoperations were necessary in 7.7 % of cases.

According to the literature, risks for reoperations include a patient age higher than 70 years, obesity, ASA3, inexperience of the workplace with operations for primary hyperparathyroidism (50 or fewer cases per year), inexperience of the operator, and unclear localization on the preoperative scintigraphic examination [2]. Another significant factor contributing to the need for reoperation is the multiple involvement of the parathyroid glands in MEN1. In our group of MEN1 patients,

reoperations were performed in 35 % of cases.

Before a reoperation, it is advisable to go through the patient's history again, focusing on familial occurrence. Multiple involvement of the parathyroid glands is present in reoperations for recurrent primary hyperparathyroidism. When multiple parathyroid diseases are suspected, a bilateral exploration of the neck is usually indicated. When a single adenoma is suspected, it is appropriate to choose a more focused approach, which reduces the risk of recurrent laryngeal nerve injury and the risk of permanent hypocalcemia. During reoperations, permanent recurrent laryngeal nerve paresis occurs in 6-9 % of cases, but the risk can be reduced by the use of neuromonitoring. The risks and benefits of reoperation should be discussed with the patient. In the literature, reoperations in patients with MEN1 syndrom have been reported ranging from 9 to 50 % [3,4].

Primary hyperparathyroidism in MEN1 is usually the first recognized endocrinopathy, and occurs in 5 % of patients with primary hyperparathyroidism [5]. Our study also confirms the young age of patients with MEN1 syndrome at primary surgery, with an average of 39 years (range 22–64 years) compared to 60 years in patients with sporadic primary hyperparathyroidism.

Patients with MEN1 syndrome often have multiple involvement of the parathyroid glands, and therefore subtotal parathyroidectomy with preservation of the peduncle or total parathyroidectomy with autotransplantation of the parathyroid gland is recommended for primary surgery [6].

The necessity of reoperation in patients with MEN1 syndrome is primarily dependent on recognizing the presence of this syndrome preoperatively. Genetic tests can thus be used to recognize MEN1 syndrome before surgery and to determine the appropriate surgical approach. Genetic testing should be performed in individuals undergoing surgery for primary hyperparathyroidism who are under 40 years of age, as well as in individuals who have a positive family history, or in cases with multiple involvement of the parathyroid glands [7]. It is also necessary to take into account the time-consuming nature of genetic tests.

The question remains whether to perform bilateral exploration or a targeted procedure during reoperations for MEN1 syndrome. Knowledge of past performance is sometimes key to this decision. During reoperation, the last parathyroid gland may be removed and permanent hypocalcemia may occur, with reported frequencies ranging from 0–15 % of cases [8,9,10].

Other complications such as bleeding or infection are the same as in primary surgery.

Reoperations are technically more demanding and should therefore be performed in specialized centers where genetic testing for MEN1 syndrome is available. The cure rate in such centers can reach 93–97 % [11,12].

Conclusion

Patients with multiple endocrine neoplasia syndrome have a higher risk of needing reoperations. In selected cases, it is necessary to carry out genetic tests to rule out MEN1 syndrome, as genetic confirmation of MEN1 should lead to a change in surgical tactics. These patients should primarily be operated in a specialized center.

Conflict of Interest

There is no conflict of interest.

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