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A follow-up study of patients with MEN syndromes — five case reports

Ocena chorych z zespołem MEN — 5 przypadków

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Abstract

Introduction: The aim of the study was evaluation of the results of surgical treatment in patients with hyperparathyroidism related to MEN syndrome.

Material and methods: Five patients with MEN-related hyperparathyroidism were operated between January 1, 2010 and December 31, 2016 — three women (60%) and two men (40%) aged between 17 and 72 years (mean 41.6 years). MEN1 syndrome was diagnosed in four patients and MEN2 only once. Pre- and postoperative results of PTH levels and serum calcium values were compared.

Results: The mean preoperative serum PTH level was 215.56 pg/ml (from 113.4 to 376.6 pg/ml), whereas the mean preoperative serum calcium concentration was 1.40 mmol/l (from 1.15 to 1.50 mmol/l). Patients with MEN1 syndrome had three and two thirds of parathyroid gland taken in these three cases, including two cases with a partial thyroid removal, and the last one had a parathyroid biopsy performed. A patient with MEN2 syndrome had one parathyroid gland excised and Dunhill surgery of the thyroid gland performed. A diagnosis of the parathyroid adenoma accompanying medullary thyroid cancer required additional resections for the diseased thyroid parenchyma and the neck dissection. Postoperatively, we reported decreased secretion of both PTHs, ranging from 2.0 to 18.4 pg/ml (a mean serum PTH concentration 6.72 pg/ml), and serum calcium concentration between 0.9 and 1.25 mmol/l (a mean serum calcium concentration 1.11 mmol/l). One patient (25%) with MEN 1 developed recurrent hyperparathyroidism five years after the surgery. The patient was reoperated. The rest of the parathyroid gland was removed with an implantation into separated muscle pockets in the anterior forearm muscles.

Conclusions:

1. MEN syndrome is a rare cause of primary hyperparathyroidism.
2. Subtotal parathyroidectomy helps to restore normal calcium metabolism.
3. Recurrence of hyperparathyroidism in patients with MEN syndrome requires total parathyroidectomy with an autotransplantation into the anterior forearm muscles. **(Endokrynol Pol 2018; 69 (2): 163–167)**

Key words: *multiple endocrine neoplasia, parathyroid neoplasms, hyperparathyroidism, parathyroid glands, parathyroidectomy, thyroid gland, calcium metabolism*

Streszczenie

Wstęp: Celem pracy była ocena wyników leczenia chirurgicznego pacjentów z nadczynnością przytarczyc w przebiegu zespołu MEN.

Materiał i metodyka: Zespół MEN stwierdzono u 3 kobiet i 2 mężczyzn w wieku 17–72 lata (średnio 41,6) spośród 419 chorych operowanych w latach 2010–2016 z powodu pierwotnej nadczynności przytarczyc. Zespół MEN1 zdiagnozowano u 4 chorych zaś MEN2 jednej. W pracy porównano stężenia parathormonu (PTH) i wapnia zjonizowanego (Ca^{2+}) w surowicy krwi przed i po operacji.

Wyniki: U chorych z zespołem MEN średnie przedoperacyjne stężenie PTH wyniosło 215,56 pg/ml a Ca^{2+} 1,4 mmol/l. W przebiegu MEN1 u trzech chorych wycięto 3 i 2/3 przytarczyc, u jednego zaś jedną przytarczycę z biopsją pozostałych. U chorej z MEN2 wycięto jedną przytarczycę z całkowitym wycięciem tarczycy i węzłów chłonnych szyi. Pooperacyjnie odnotowano spadek stężeń PTH do wartości średnio 6,72 pg/ml oraz Ca^{2+} do 1,11 mmol/l w surowicy krwi. U jednego chorego z zespołem MEN1 doszło do nawrotu nadczynności przytarczyc po 5 latach od operacji. Chory ponownie operowany — wycięcie pozostałej przytarczycy z autotransplantacją fragmentu do mięśni przedramienia.

Wnioski:

1. Zespół MEN jest rzadką przyczyną nadczynności przytarczyc
2. Częściowa subtotalna resekcja przytarczyc przywraca prawidłowy metabolizm wapnia.
3. Nawrót nadczynności przytarczyc u pacjentów z zespołem MEN wymaga całkowitej resekcji przytarczyc z autotransplantacją fragmentu do mięśni przedramienia. **(Endokrynol Pol 2018; 69 (2): 163–167)**

Słowa kluczowe: *mnoga gruczolakowatość wewnątrzwydzielnicza, nadczynność przytarczyc, rak tarczycy, paratyreoidektomia*

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Table I. *Patients operated due to MEN syndrome — characteristic of polyglandular pathology*
Tabela I. *Operowani pacjenci z zespołem MEN — charakterystyka niedoczynności wielogruczołowej*

			Endocrine gland pathology					
No	**Sex**	**Age**	**Parathyroid**	**Thyroid**	**Pituitary**	**Pancreas**	**Adrenal gland**	**Ovaries**
1	M	26	PHPT — hyperplasia 3	Nodular goitre	Prolactinoma	Gastrinoma		
2	F	17	PHPT — hyperplasia 1	Nodular goitre	Somatotropinoma			PCOD
3	F	72	PHPT — hyperplasia 3	Nodular goitre	Somatotropinoma	Insulinoma	Non-functional adenoma	
4	M	33	PHPT — hyperplasia 3	Nodular goitre				
5	F	60	PHPT — adenoma	Medullar carcinoma (RET+)			Bilateral adenoma non-functional	

Introduction

Primary hyperparathyroidism (PHPT) is most frequently found (95% of patients) in sporadic form [1, 2], whereas it appears rarely (5% of patients) in familial form as a syndrome of multiple endocrine neoplasia (MEN). The appearance of MEN is connected with MEN 1 gene mutation and leads to Wermer syndrome or that of RET gene in MEN 2A syndrome [3].

Surgical treatment is the most effective method of dealing with PHPT, and its extent depends on the type of pathology within parathyroid glands [4–6].

The aim of the study

The aim of the study was to evaluate the follow-up studies of the surgical treatment of patients with PHPT related to multiple endocrine neoplasia.

Material and methods

A total of 419 patients were operated on for various types of hyperparathyroidism between January 1, 2010 and December 31, 2016. Five of them (1.2%) were diagnosed with a multiple endocrine neoplasia syndrome confirmed by genetic tests. The latter group consisted of three women (60%) and two men (40%) aged 17–72 years, with a mean age 41.6 years. MEN 1 syndrome was diagnosed in four patients, and MEN2 in one. Localisation of the lesions was stated on MIBI-SPECT scintigraphy with preoperative USG. Moreover, PTH, ionised calcium, creatinine level, and glomerular filtration rate (GFR) were measured. All patients were operated under general anaesthesia by classic method. Bilateral neck exploration was done, and all parathyroid glands were identified. Preoperative results were compared with those obtained postoperatively.

Results

Tumours of other endocrine organs in MEN1 disease were identified in group of four patients with primary hyperparathyroidism (Tab. I). Concomitance of pituitary tumour was seen in three patients — twice somatotropinoma and once prolactinoma. Two patients were treated for pancreatic tumour — one insulinoma and one gastrinoma. Concomitance of adrenal tumour was noticed in one patient. Preoperative serum PTH value was 113.4–218.0 pg/ml (mean 188.35 pg/ml) in MEN1 patients, whereas Ca^{2+} was 1.15–1.45 mmol/l (mean 1.29 mmol/l). Before operation all patients were treated with cinacalcet. Three of them underwent total resection of three affected glands with partial resection of the fourth and subtotal resection of the thyroid gland, and bilateral neck exploration in two cases. The one patient underwent total resection of one parathyroid gland. Surgical biopsy of the remaining glands was done. Histopathological examinations revealed hyperplasia of all resected parathyroid glands. On the first postoperative day PTH level decreased to 2.0–18.4 pg/ml (mean 8.2 pg/ml), whereas Ca^{2+} decreased to 1.10–1.25 mmol/l (mean 1.14 mmol/l). Recurrent hyperparathyroidism developed after five years in one patient (33.3%). PTH grew up to 84.89 pg/ml and total Ca to 2.57 mmol/l. He was reoperated, and the gland was resected. Part of it was implanted into the patient's forearm muscle and the rest was covered for later use. A rapid PTH value drop was noticed to 2.34 pg/ml and Ca^{2+} to 1.06 mmol/l.

MEN2A syndrome was diagnosed in one patient operated for primary hyperparathyroidism after surgical treatment and histopathological verification. The MEN2 female patient revealed preoperative serum PTH value 376.6 pg/ml, whereas ionised calcium was 1.27 mmol/l. She underwent total resection of the parathyroid adenoma and Dunhill operation. Histopathological examination revealed a parathyroid adenoma with concomitant thyroid medullary cancer. Finally, resection of the remaining thyroid stump was decided together with resection of the middle compartment and lateral compartments of the neck. Genetic examination revealed familial papillary thyroid carcinoma with RET proto-oncogene mutation.

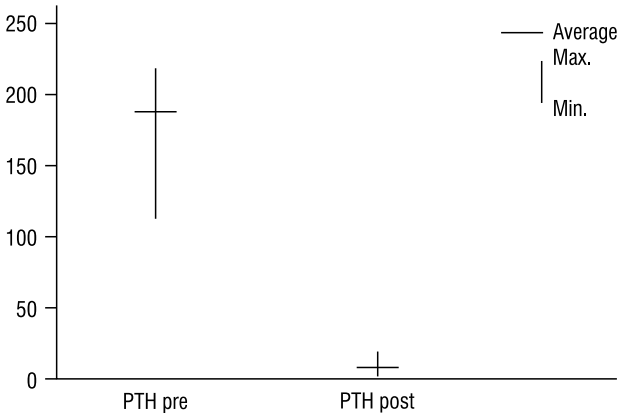

Figure 1. *Pre- and postoperative PTH levels in blood serum in patients treated for MEN1*

Rycina 1. *Stężenie PTH w surowicy krwi przed i pooperacyjne u chorych operowanych z powodu MEN1*

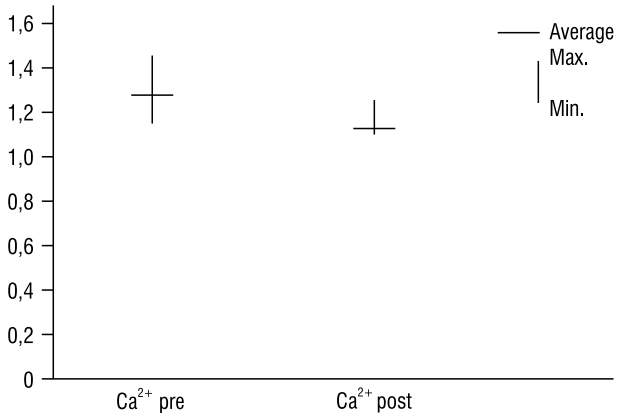

Figure 2. *Pre- and postoperative Ca2+ levels in serum in patients treated for MEN1*

Rycina 2. *Przed- i pooperacyjne stężenie Ca2+ w surowicy krwi u chorych operowanych z powodu MEN1*

A drop of PTH was noted (to 2.5 pg/ml) and Ca^{2+} (to 0.9 mmol/l). After four years she is alive with no symptoms of the disease or cancer. Calcitonin 18.7 pg/ml (N < 11.5) and carcino embryonic antigen CEA 1.54 ng/ml (N < 5) levels are both postoperatively stagnant. (not suspicious for carcinoma tumour — no data before operation). Imaging explorations (CT scan and ultrasound) did not reveal a relapse of the regional thyroid carcinoma. Abdominal CT scan confirmed non-functional adrenal adenomas.

Discussion

Clinical symptoms of PHPT are often the first fully recognised signs of endocrinopathy that can be found in multiple endocrine neoplasia [7]. The responsible factor is often hyperplasia of the glands, which we observed not only in all patients operated with MEN 1 in our hospital, but also with adenoma, as in the case of the patient with MEN 2A [1, 3, 8]. Another cause of the hyperparathyroidism can be connected with parathyroid cancer [3, 9, 10].

Nowadays the surgical treatment of PHPT is the treatment of choice. However, results of such treatment are often too difficult to predict, for many reasons, both diagnostic and therapeutic, that a surgeon must face. The main goal of such an operation is to guarantee normocalcaemia and minimal risk of recurrence [7]. In the treatment of a recurrence, precise and easy identification of the affected gland is necessary [6]. On the other hand, the surgeon should protect the patient against persistent and permanent calcium deficiency, which is often very troublesome for the patient [11].

Very crucial is the surgeon's experience [11, 12]. Before surgery precise imaging diagnostics should be performed to consider the number and location of the affected parathyroid glands. Preoperative USG of the neck and SPECT MIBI-TC scintigraphy of parathyroid glands usually help to localise the affected glands [13, 14]. Concomitant lesions within the thyroid gland may also play a role when making a choice of the operative method [13]. The presence of focal lesions or changes in the thyroid gland may require a fine-needle biopsy, in addition. In such a situation, we are convinced that fine-needle biopsy should be guided when the parathyroid gland is revealed. We fear that parathyroid cells might be disseminated. If a malignant lesion is suspected a total resection of the thyroid gland with a cervical lymphadenectomy is performed [8, 15, 16]. This is confirmed by our observations. All three MEN1 patients required additional partial resection of the thyroid gland, but one MEN 2A female required radical resection of the thyroid gland accompanied by resection of cervical lymph nodes.

Minimally invasive techniques have become more and more popular recently [17, 18]. There are still discussions among surgeons on the choice of either conventional techniques with bilateral identification of the parathyroid gland or minimally invasive methods. Hypertrophy of the parathyroid glands (as we observed in all MEN 1 patients in our study), the presence of multiple adenomatous lesions leading to PHPT, or the absence of preoperative clear location of the affected glands required a conventional technique, which was a method of choice [11].

On the other hand, preoperative identification of the affected parathyroid glands may require minimally invasive techniques. However, it is important to remember that hyperplastic lesions, diagnosed by scintigraphy, usually refer only to the dominant gland [14]. Therefore the efficacy of the operative treatment should be verified by intraoperative blood serum parathormone

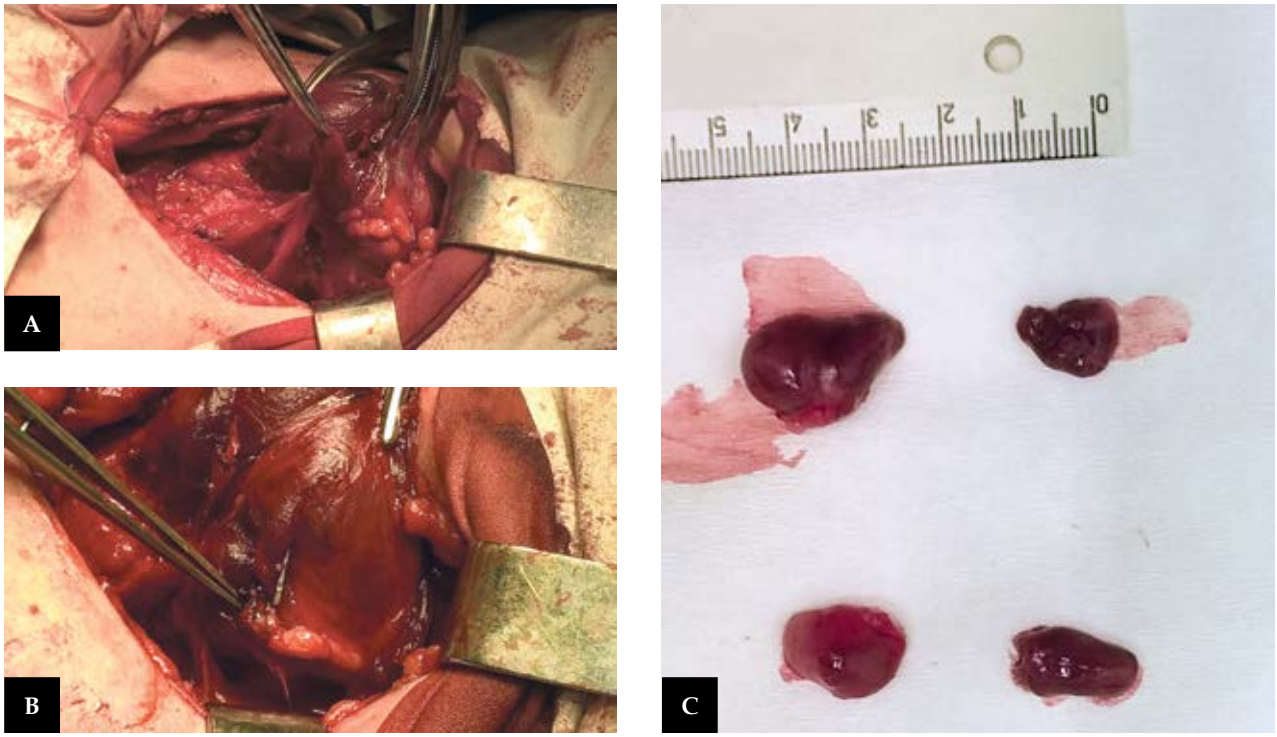

Figure 3. *Intraoperative view of parathyroid gland in MEN 1 syndrome.* ***A.*** *Enlarged parathyroid gland prepared for partial resection;* ***B.*** *State after partial parathyroid resection — inserted titanium clip;* ***C.*** *3 and 3/4 parathyroid glands with hyperplasia — post resection view*

Rycina 3. *Obraz śródoperacyjny przytarczyc w zespole MEN 1.* ***A.*** *Zmieniona rozrostowo przytarczyca wypreparowana do częściowej resekcji;* ***B.*** *Stan po resekcji częściowej przytarczycy — założony klips tytanowy;* ***C.*** *Zresekowane 3 i ¾ przytarczyce zmienione rozrostowo*

concentration [7, 19]. This may impose a decision to finish the operation or to continue exploration of the neck in order to search for the cause of the disease. It is essential to determine whether the symptoms of hyperparathyroidism persist or recur because each subsequent surgical intervention will increase the risk of complications developing, particularly in recurrent laryngeal nerves. Therefore, we recommended specifically the use of neuromonitoring.

The extent of surgical HPT treatment in MEN syndromes has not been determined yet, although it has an influence on the treatment efficacy. Some surgeons prefer a subtotal parathyroidectomy and others recommend a total resection of parathyroid glands accompanied by autotransplantation on forearm muscles [5, 7, 15, 20]. Each of the techniques is part of the operation for recurrent hyperparathyroidism [4, 21], probably caused by supernumerary glands in ectopic position and oversized stump of the partially resected gland. Some surgeons decide to perform thymus resection, in addition [6, 22]. Another cause of recurrent hyperparathyroidism may also be connected with an autologous transplant on the forearm. Surgeons who prefer total parathyroidectomy followed by autotransplantation on forearm muscles indicate that it is easy to remove afterwards, when HP recurrence is diagnosed. They also point out that it may be technically easy to identify the transformed parathyroid gland, and the number of postoperative complications, such as recurrent laryngeal nerve palsy, lymphorrhagia, or Horner's syndrome, might be limited. During the process of subtotal parathyroidectomy, it is very useful to place a marker in the region of the left gland in the form of a non-absorbable suture of titanic clip in order to identify the parathyroid recurrence [6]. It is also very important to become familiar with all the data related to the previous surgeries as well as the diagnostic imaging test results. There are some surgeons who state that minimally invasive techniques are adequate to remove the gland with the macroscopic change while the risk of a recurrence is small and usually distant in time [17, 18]. Another theory emphasises that subtotal parathyroidectomy is more comfortable than the total resection of all the glands accompanied by autotransplantation of the parathyroid homogenate to the forearm muscle, even though such a procedure requires securing of the material for further use by a high percentage of uncomfortable hypocalcaemia [23]. Nevertheless, it requires additional highly specialised laboratory techniques. The operative treatment of parathyroid glands as a component of MEN should be managed by highly specialised centres that are provided with experienced surgical staff.

Conclusions

1. MEN is a rare cause of primary hyperparathyroidism.
2. Subtotal parathyroidectomy helps to restore normal calcium metabolism.
3. HPT recurrence in MEN patients requires total parathyroidectomy probably followed by autotransplantation to forearm muscles.

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