



Research Article

DOI: 10.36959/608/461

Post-Parathyroidectomy Secondary Hyperparathyroidism in Patients with Primary Hyperparathyroidism Treated by Focused Parathyroidectomy: A Retrospective Case Study

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Abstract

Background: Focused parathyroidectomy has become the surgery of choice for sporadic primary hyperparathyroidism. In certain patients after apparently successful parathyroidectomy, parathyroid hormone (PTH) remains to be elevated despite normalized serum calcium, known as post-parathyroidectomy secondary hyperparathyroidism (PPSH). This study aims to investigate the factors related to PPSH. In addition, the natural course of PPSH will be evaluated and the factors for spontaneous resolution of PPSH analyzed.

Methods: A retrospective study was conducted. 116 patients undergoing focused parathyroidectomy for sporadic primary hyperparathyroidism in our hospital during the period between 2008 and 2018 were reviewed. Multivariate analysis was conducted on parameters including age at operation, gender, adenoma weight, pre-operative serum calcium, PTH, vitamin D, alkaline phosphatase, creatinine.

Results: 32 patients (27.6%) developed post-parathyroidectomy secondary hyperparathyroidism. Spontaneous recovery occurred in 24 patients (75%) with PPSH. On multivariate analysis, vitamin D levels ($p = 0.041$), pre-op PTH ($p = 0.018$) and adenoma weight ($p = 0.039$) are found to be significant factors of eventual spontaneous recovery from PPSH.

Conclusion: PPSH is a common phenomenon. Most cases resolve spontaneously. Higher levels of vitamin D may fuel the resolution of PPSH. Peri-operative vitamin D levels measurement and replenishment of vitamin D deficiency may have preventive and therapeutic bearings against PPSH.

Keywords

Focused parathyroidectomy, Primary hyperparathyroidism, Post-parathyroidectomy, Secondary hyperparathyroidism

Introduction

Majority of cases of sporadic primary hyperparathyroidism (PHPT) are ascribed to solitary parathyroid adenoma [1]. Parathyroidectomy is the mainstay of treatment in patients with hypercalcemic PHPT. Focused parathyroidectomy by removal of parathyroid adenoma, as localized on pre-operative imaging, successfully results in the normalization of serum calcium levels [2]. Successful parathyroidectomy is defined as normalized calcium levels at 6 months post-parathyroidectomy. However, in certain patients, parathyroid hormone (PTH) may remain elevated after apparently successful parathyroidectomy despite normalization of serum calcium levels, we label the phenomenon as post-parathyroidectomy secondary hyperparathyroidism (PPSH).

The mean prevalence of PPSH was 23.5%, ranging from 3 to 46% [3]. Higher pre-operative PTH level, lower pre-operative vitamin D level, lower pre-operative creatinine

clearance, and greater adenoma weight have been associated with PPSH [4-7].

Previous studies were mainly Caucasian series. Moreover, the surgical approach of parathyroidectomy in older studies

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Accepted: March 03, 2022

Published online: March 05, 2022

Citation: Lin AS, Chow T (2022) Post-Parathyroidectomy Secondary Hyperparathyroidism in Patients with Primary Hyperparathyroidism Treated by Focused Parathyroidectomy: A Retrospective Case Study. *J Surgical Endocrinol* 4(1):125-128

was heterogenous including either bilateral neck exploration, unilateral neck exploration or focused parathyroidectomy. Therefore we have conducted a retrospective study in patients treated by focused parathyroidectomy for sporadic PHPT in a regional hospital in Hong Kong, aiming to investigate the risk factors related to PPSH for a Chinese population. In addition, the natural course of PPSH will be delineated and the factors for spontaneous resolution of PPSH analyzed.

Methods

The data of patients diagnosed with sporadic primary hyperparathyroidism who underwent focused parathyroidectomy from January 2008 to December 2018 were retrospectively retrieved from our hospital database. Patients with renal failure, secondary hyperparathyroidism, familial hyperparathyroidism, non-Chinese patients and patients under the age of 18 were excluded. Parameters including age at operation, gender, adenoma weight, surgical approach, pre-operative serum calcium, PTH, vitamin D, alkaline phosphatase (ALP), creatinine levels were evaluated.

Patients with PPSH were further stratified into patients with persistently elevated PTH levels, and patients with eventually normalized PTH levels.

Data were analyzed by student's T test for continuous variables and a multivariate analysis was performed. Chi-square tests were used for categorical variables. The results were considered statistically significant if the p-value was less than 0.05. SPSS version 23 was used for data computation.

Results

A total of 116 patients fulfilling the enrollment criteria were identified for evaluation. 98 patients (84%) were treated by focused parathyroidectomy under LA with cervical plexus block, while the remaining patients underwent bilateral neck exploration for reasons including concomitant thyroid nodule, toxic goiter or double parathyroid adenoma. All patients are Chinese. The mean follow-up duration is 20-months.

32 patients (27%) developed PPSH. Among these patients, PTH levels eventually spontaneously normalized in 24 (75%) patients. Time required for normalization of PTH varies from 4 months to 96 months, with a mean duration of 23.8 months. Resolution of PPSH was spontaneous without additional

medical treatment. PTH levels remain persistently elevated in 8 out of 32 (25%) patients with PPSH, of which 1 patient eventually developed recurrent primary hyperparathyroidism 7 months post-operation.

Multivariate analysis was performed comparing patients with and without PPSH. There is no statistically significant difference between the two groups (PPSH vs. non-PPSH) of patients concerning pre-operative PTH ($p = 0.695$), Calcium ($p = 0.748$), Creatinine ($p = 0.156$), ALP ($p = 0.669$), age at operation ($p = 0.148$), adenoma weight ($p = 0.566$) and vitamin D ($p = 0.158$) (Table 1).

When comparing patients with persistent elevation of PTH versus patients with eventual spontaneous normalization of PTH levels, in patients in whom PTH levels eventually normalized, vitamin D levels ($p = 0.041$) were found to be significantly higher, and pre-operative PTH ($p = 0.018$) and adenoma weight ($p = 0.039$) were found to be significantly lower, while there is no statistically significant difference in the other parameters.

There is no significant difference in the occurrence and resolution of PPSH for gender and surgical approach in chi-squared tests (Table 2).

Discussion

PPSH is a common phenomenon, occurring in 27% of patients in our hospital. Over time, only 1 out of 32 patients (3%) developed recurrent primary hyperparathyroidism. Most cases of PPSH resolve (75%) without additional treatment.

Relationship between PPSH and the recurrence of PHPT remains controversial. While Goldfarb, et al. [8] and Lang, et al. [9] showed that PPSH did not predict recurrence of PHPT, Ning L [10] reported the incidence of recurrent PHPT was significantly higher in patients with PPSH.

The cause of PPSH is still not well understood. It was postulated in literature that PPSH is the reflection of bone remineralization after parathyroidectomy in individuals with prolonged exposure to supraphysiological levels of parathyroid hormone [11,12], Vitamin D deficiency [13] and decreased renal parathyroid hormone sensitivity due to renal insufficiency had also been described as attributing factors to PPSH [14].

Table 1: Multivariate analysis of patients with and without PPSH.

Parameters	PPSH (N = 20)	Without PPSH (N = 46)	P value
Pre-op PTH (pmol/ L)	21.2	24.4	0.695
Pre-op Calcium (mmol/ L)	2.691	2.706	0.748
Pre-op Creatinine (umol/L)	88	75	0.156
ALP (IU/ L)	134	154	0.669
Age at operation	66	61	0.148
Adenoma weight (g)	1.83	2.40	0.566
Vitamin D (nmol/ L)	67	57	0.158

Table 2: Multivariate analysis of PPSH patients with and without normalization of PTH levels.

Parameters	Persistent PPSH (N = 5)	PPSH resolved (N = 20)	P value
Pre-op PTH (pmol/L)	38.4	20.2	0.018
Pre-op Calcium (mmol/L)	2.76	2.67	0.222
Pre-op Creatinine (umol/L)	88	86	0.931
ALP (IU/L)	155	131	0.386
Age at operation	66	65	0.83
Adenoma weight (g)	3.07	1.39	0.039
Vitamin D (nmol/L)	40	69.85	0.041

Physiological adverse effects of PPSH had also been studied. Vestergaard, et al. [15] demonstrated that the frequency of cardiovascular disease including hypertension, congestive heart failure, myocardial infarction and angina pectoris is higher in patients with PPSH than those with normal PTH levels post-parathyroidectomy for PHPT. Pathak, et al. [16] reported that elevated parathyroid hormone after parathyroidectomy delays symptom improvement for symptoms such as anxiety, thirst, constipation, and polyuria.

In our study, vitamin D deficiency was found to be a significant factor in the development of persistent PPSH, leading us to consider the need of vitamin D replenishment for patients who were revealed to have vitamin D deficiency before or after parathyroidectomy for PHPT. Beyer, et al. [17] demonstrated in a retrospective study of 86 patients undergoing parathyroidectomy for PHPT that the incidence of PPSH was significantly lower for patients who received Calcitriol. This echoes our study's results.

Limitations of this study include the small sample size and the intrinsic limitation of a retrospective study such as missing data etc.

To conclude, post-parathyroidectomy secondary hyperparathyroidism is a common phenomenon. Most cases resolve spontaneously. Higher levels of vitamin D may fuel the resolution of PPSH. Peri-operative vitamin D levels measurement and replenishment of vitamin D deficiency may have preventive and therapeutic bearings against PPSH.

Acknowledgements

Specialty Outpatient Clinic nurses and staff, and secretaries of Department of Surgery of United Christian Hospital.

Authors Declaration

There is no financial support or conflict of interest to be declared.

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DOI: 10.36959/608/461

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