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Decrease in the Prevalence of Pancreatitis Associated with Primary Hyperparathyroidism: Experience at a Tertiary Referral Center

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ABSTRACT

Background: Hypercalcemia is a rare but well recognized cause of acute and chronic pancreatitis. Hypercalcemia-related pancreatitis is mainly caused by primary hyperparathyroidism. The prevalence of pancreatitis in hyperparathyroidism varies worldwide and additional disease-modifying factors may play a role in its development. In 1988 the prevalence of pancreatitis secondary to primary hyperparathyroidism at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ), a referral center in Mexico City, was 12.1% (95% CI: 6.7-21). **Objective**: To describe the current prevalence of pancreatitis secondary to primary hyperparathyroidism at the INCMNSZ. **Methods**: We reviewed 385 cases of primary hyperparathyroidism seen at the hospital between 1987 and 2012. **Results**: 26 cases with acute or chronic pancreatitis associated with primary hyperparathyroidism were documented, with a prevalence of 6.7% (95% CI: 4.6-9.7), which was lower than the 12.1% previously reported. In the present study, 20% had a history of alcohol consumption, 10% of gallstones, and 20% of ureteral calculi, compared with the previously reported 32.0, 34.6, and 40.0%, respectively. The average calcium levels were 13.1 and 13.8 mg/dl in the previous and current series, respectively. **Conclusions**: We found a decrease in the prevalence of pancreatitis associated with primary hyperparathyroidism from 12.1% (95% CI: 6.7-21) to 6.7% (95% CI: 4.6-9.7). (REV INVES CLIN. 2015;67:177-81)

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INTRODUCTION

Hypercalcemia is a rare but well recognized cause of acute and chronic pancreatitis[1]. Pancreatitis due to hypercalcemia is mainly caused by primary hyperparathyroidism (PHPT)[2]. However, the prevalence of pancreatitis in patients with PHPT is variable. Most studies report an association between both entities, but others have found a frequency similar to that of the normal population[3-5]. These divergent observations suggest that additional disease-modifying factors may play an important role in the development of pancreatitis in patients with PHPT. Molecular studies have reported that the elevation of cytosolic calcium triggers acute pancreatitis[6]. Other reports have shown that a combination of hypercalcemia and genetic variants in *SPINK1* and *CFTR*, among other genes, increase the risk of developing pancreatitis in patients with PHPT[2].

In 1988 a prevalence of 12.1% (range, 6.7-21.0) of pancreatitis associated with hyperparathyroidism at the National Institute of Medical Sciences and Nutrition Salvador Zubirán (INCMNSZ) was reported[7]. Currently, PHPT is diagnosed more frequently and most patients are asymptomatic, but there are still severe cases of PHPT with pancreatitis related to this condition. Pancreatitis is associated with significant morbidity and mortality and the correction of associated factors, such as hypercalcemia, is essential to avoid recurrent episodes. We hypothesize that the prevalence of pancreatitis related to PHPT has decreased due to a higher number of cases of hyperparathyroidism. The aim of this report is to describe the current prevalence of pancreatitis associated to hyperparathyroidism at the INCMNSZ.

MATERIAL AND METHODS

A search of the clinical records was conducted using the International Statistical Classification of Diseases and Related Health Problems. For clinical records between 1987 and 1998, the 9th Revision was used, including the following codes: 252.0 Hyperparathyroidism, and 275.4 Disorders of calcium metabolism. For records from 1999 to 2012, the 10th Revision was utilized, with the following codes: E.20.0 Primary hyperparathyroidism; E21.1 Secondary hyperparathyroidism; E21.2 Other hyperparathyroidism and tertiary hyperparathyroidism; E21.3 Hyperparathyroidism, unspecified; E21.4 Other specified disorders of parathyroid gland; E21.5 Disorder of parathyroid gland, unspecified; D35.1 Benign neoplasm of parathyroid gland.

Cases with PHPT and pancreatitis were selected. Acute or chronic pancreatitis was recognized in those patients with a previous pancreatitis episode prior to their admission to our institution or in those who developed pancreatitis during their follow-up. Demographic and biochemical variables were recorded, including serum calcium, phosphorus, 25-hydroxy vitamin D, and parathyroid hormone (PTH). Variables comprising presence of ureteral calculi and factors associated with pancreatitis were also documented. The average follow-up time of the cases was also recorded.

Statistical analysis

Distribution of dimensional variables was analyzed with the Shapiro-Wilk test, and means and standard deviations or medians and interquartile ranges were used as appropriate for their description. Categorical variables were reported as percentages. The prevalence of pancreatitis related to PHPT was calculated and compared with the previously reported.

Statistical analysis was performed using SPSS version 21 program.

RESULTS

From 1987 to 2012, a total of 385 patients diagnosed with PHPT were identified. Of them, 26 were considered to have pancreatitis. Five patients with hypercalcemia were not included because PHPT diagnosis could not be established either with PTH determination or by histological analysis. The 26 identified cases represent a prevalence of 6.7% (95% CI: 4.6-9.7).

Age at diagnosis of PHPT was 43.5 ± 15.3 years (range, 19-70), 69% of the cases were male, 42.3% had a history of alcohol consumption, 34.6% had concomitantly gallstones, and 42.3% ureteral calculi. In the previous series, the reported age was 32.1 ± 13.8 (range, 17-55) years while 20, 10, and 20% had a history of alcohol consumption, gallstones, and ureteral calculi, respectively.

The mean age at the first episode of pancreatitis was 41.5 ± 15.0 years (range, 18-70), 14 patients developed

Table 1. Characteristics of the patients with pancreatitis secondary to primary hyperparathyroidism in the current and previous reports

Patient characteristics	Years 1987-2012 (n = 26)	Years 1955-1984 (n = 10)
Male	18 (69)	4 (40)
Age at diagnosis of PHPT, years	43.5 ± 15.3	32.1 ± 13.8
Age at diagnosis of pancreatitis, years	41.5 ± 15.0	NA
Alcohol consumption	11 (42.3)	2 (20)
Gallstones	9 (34.6)	1 (10)
Reno-ureteral calculi	11 (42.3)	2 (20)
Recurrent pancreatitis	8 (30.1)	NA
Calcium, mg/dl*	13.8 ± 2.0	13.1
Phosphorus, mg/dl†	2.6 ± 0.6	2.4
Parathyroid hormone, pg/ml‡	269 (172-351)	NA
25-hydroxy vitamin D, ng/ml§	16.0 ± 8.9	NA

Data are expressed as number (%), mean ± standard deviation, or median (interquartile range).
*Obtained in 22 patients.
†obtained in 17 patients.
‡obtained in 23 patients.
§obtained in nine patients.
PHPT: primary hyperparathyroidism;
NA: not available.

pancreatitis before the diagnosis of PHPT; in nine cases the diagnoses were made simultaneously, two cases presented pancreatitis after the diagnosis of PHPT, and in one case it was not possible to document these dates. Eight patients (30.1%) had more than one episode of pancreatitis. Of the eight patients with recurrent pancreatitis, four had two events, one had three, two had four, and one patient had five episodes.

The average calcium and phosphorus levels determined during the episode of pancreatitis (determined in 22 and 17 patients, respectively) were 13.8 ± 2.0 mg/dl (range, 11-19) and 2.6 ± 0.6 mg/dl (range, 2-4). In the previous report of 1988, calcium levels were 13.1 mg/dl (range, 10.8-16.0) and phosphorus levels were 2.4 mg/dl (range, 2.1-3.0).

The median PTH level, documented in 23 patients, was 269 (172-351) pg/ml (range, 78-1,355), and the 25-hydroxy vitamin D level (in nine patients) was 16.0 ± 8.9 ng/ml (range, 7-38). These parameters were obtained after the last episode of pancreatitis.

Cases in which calcium or PTH levels were not available in the clinical records were included only if they had a histopathological confirmation of PHPT. Table 1 shows characteristics of the patients with pancreatitis associated with PHPT in both series.

In six patients surgery was not performed; one of them had a diagnosis of parathyroid carcinoma. Of the patients with a histopathological diagnosis, 15 (57.7%) had parathyroid adenoma, three (11.5%) had parathyroid hyperplasia, and two (7.7%) had parathyroid carcinoma. None of these cases developed pancreatitis after surgical treatment. Two patients were diagnosed with type 1 multiple endocrine neoplasia. The average follow-up time of the cases was 7.3 years.

DISCUSSION

In this report, conducted at a referral center, we found a prevalence of pancreatitis associated with hyperparathyroidism of 6.7% (95% CI: 4.6-9.7), which is lower than the previously reported 12.1% (95% CI: 6.7-21.0)[7].

In the present series, 385 cases of PHPT were identified in a period of 25 years. In contrast, the previous study reported only 82 cases of PHPT in a period of 30 years (1955-1984), a difference that may be attributed to an increased diagnosis of hyperparathyroidism. In addition, the previous report only included patients with PHPT that were surgically treated.

The frequency of pancreatitis associated with hyperparathyroidism in other published series of diverse

Table 2. Reported frequencies of pancreatitis associated with hyperparathyroidism

Author	Year	Hyperparathyroidism cases (n)	Pancreatitis cases n (%)
Narayan, et al.[12]	2015	177	13 (7.3)
Shah, et al.[13]	2014	153	27 (17.6)
Felderbauer, et al.[10]	2011	1,259	57 (4.5)
Khoo, et al.[11]	2009	684	10 (1.5)
Bhadada, et al.[14]	2008	59	9 (15.2)
Jacob, et al.[15]	2006	101	13 (12.9)
Agarwal, et al.[3]	2003	87	6 (6.9)
Carnaille, et al.[16]	1998	1,224	40 (3.3)
Sheperd, et al.[17]	1996	137	7 (5.1)
Koppelberg, et al.[5]	1994	234	13 (5.6)
Sitges-Serra, et al.[18]	1988	86	7 (8.1)
Bess, et al.[4]	1980	1,153	17 (1.5)

populations is on average 3.6%, with a prevalence that varies widely, ranging from 1.5 to 15.3%[8]. Table 2 summarizes reported frequencies of pancreatitis associated with hyperparathyroidism.

When comparing the characteristics of the patients in both reports, we found that the average age at diagnosis found in the previous series was 32.1 years (range, 17-55)[7], while the patients included in this series were older, with a mean age of 43.5, ranging from 19 to 70 years. Age at diagnosis of pancreatitis was 41.5 years, indicating that in most of the cases the diagnosis of PHPT was established after the first pancreatitis event.

In the previous report, the mean calcium was 13.1 mg/dl (range, 10.8-16.0) and in the current review we found a mean calcium level of 13.8 mg/dl (range, 11-19). Ureteral calculi were reported in 20% of the previous cases and here we found that 40% of cases had this complication. Gallstones were reported in 10% and we recorded this finding in 32% of cases. Alcohol consumption was reported in 20% of cases in the previous study[7] compared with 32% in the current series.

Previously, the diagnosis of hyperparathyroidism was typically made in patients with overt clinical manifestations, including ureteral calculi, peptic ulcer, pancreatitis, and osteoporosis, among others. Routine measurement of calcium in laboratory studies began in the USA in 1974 and later in Mexico. This was associated with a significant increase in the diagnosis of asymptomatic PHPT, accompanied by a decreased risk of the associated complications[9]. In our study, we found a considerable proportion of patients with ureteral calculi in addition to pancreatitis. Furthermore, calcium serum levels were considerably higher than levels typically reported in patients with PHPT; these findings illustrate the severity of PHPT cases with coexistent pancreatitis. In addition, other studies comparing PHPT patients with and without pancreatitis, also have documented higher calcium levels[10,11].

Occasionally, hypercalcemia is not considered as a potential etiology of pancreatitis since it is an uncommon cause, and most patients with hypercalcemia do not develop pancreatitis[8]. This observation raises the question of why only some individuals with hypercalcemia develop pancreatitis. One potential explanation is that some patients have other risk factors, in addition to hypercalcemia, that make them more susceptible to develop pancreatitis. Among these risk factors are genetic variants, alcohol consumption, and gallstones. In our study, we observed that more than half (57%) of the patients presented an additional risk factor for developing pancreatitis, such as alcohol consumption and a history of gallstones[4]. Initially in some of these patients, the etiology of pancreatitis was attributed only to these coexisting factors, and some of them presented more than one episode of pancreatitis. Once the diagnosis of hyperparathyroidism was established and the appropriate treatment was provided, they did not present further episodes of pancreatitis.

The limitations of this report should be acknowledged, including its retrospective nature, which did not allow us to collect all the variables in each patient. However,

given the low frequency of pancreatitis associated with PHPT, it is difficult to conduct a prospective study with a larger number of cases. In addition, the study was conducted in a referral center; therefore, a selection bias may occur, with the risk of overlooking mild cases.

We conclude that the prevalence of pancreatitis in patients with PHPT decreased from 12.1% (95% CI: 6.7-21.0) to 6.7% (95% CI: 4.6-9.7). This was probably due to an increase in the number of cases diagnosed with PHPT as a result of the routine measurement of calcium in recent years.

DECLARATION OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology. 2001;120:682-707.
2. Felderbauer P, Karakas E, Fendrich V, et al. Pancreatitis risk in primary hyperparathyroidism: relation to mutations in the SPINK1 trypsin inhibitor (N34S) and the cystic fibrosis gene. Am J Gastroenterol. 2008;103:368-74.
3. Agarwal A, George RK, Gupta SK, Mishra SK. Pancreatitis in patients with primary hyperparathyroidism. Indian J Gastroenterol. 2003;22:224-5.
4. Bess MA, Edis AJ, van Heerden JA. Hyperparathyroidism and pancreatitis. Chance or a causal association? JAMA. 1980;243:246-7.
5. Koppelberg T, Bartsch D, Printz H, Hasse C, Rothmund M. [Pancreatitis in primary hyperparathyroidism (pHPT) is a complication of advanced pHPT]. Dtsch Med Wochenschr. 1994;119:719-24.
6. Sutton R, Criddle D, Raraty MG, Tepikin A, Neoptolemos JP, Petersen OH. Signal transduction, calcium and acute pancreatitis. Pancreatology. 2003;3:497-505.
7. Fernandez Del Castillo C, Cantu-Gonzalez G, Robles-Diaz G, Campuzano M. [Primary hyperparathyroidism and pancreatitis. Evidence for a positive association]. Rev Gastroenterol Mex. 1988;53:61-5.
8. Bai HX, Giefer M, Patel M, Orabi AI, Husain SZ. The association of primary hyperparathyroidism with pancreatitis. J Clin Gastroenterol. 2012;46:656-61.
9. Bilezikian JP, Silverberg SJ. Clinical practice. Asymptomatic primary hyperparathyroidism. N Engl J Med. 2004;350:1746-51.
10. Felderbauer P, Karakas E, Fendrich V, Lebert R, Bartsch DK, Bulut K. Multifactorial genesis of pancreatitis in primary hyperparathyroidism: evidence for "protective" (PRSS2) and "destructive" (CTRC) genetic factors. Exp Clin Endocrinol Diabetes. 2011;119:26-9.
11. Khoo TK, Vege SS, Abu-Lebdeh HS, Ryu E, Nadeem S, Wermers RA. Acute pancreatitis in primary hyperparathyroidism: a population-based study. J Clin Endocrinol Metab. 2009;94:2115-8.
12. Narayan SD, Kumar Gupta S, Kumari N, Krishani N, Chand G, Mishra A, et al. Primary hyperparathyroidism presenting as hypercalcemic crisis: Twenty-year experience. Indian J Endocr Metab 2015;19:100-5.
13. Shah VN, Kumar BS, Bhansali A, et al. Effect of gender, biochemical parameters & parathyroid surgery on gastrointestinal manifestations of symptomatic primary hyperparathyroidism. Indian J Med Res. 2014;139:279-84.
14. Bhadada SK, Udawat HP, Bhansahi A, Rana SS, Sinha SK, Bhasin DK. Chronic pancreatitis in primary hyperparathyroidism; comparison with alcoholic and idiopathic chronic pancreatitis. J Gastroenterol Hepatol. 2008;23:959-64.
15. Jacob JJ, John M, Thomas N, et al. Does hyperparathyroidism cause pancreatitis? A South Indian experience and a review of published work. ANZ J Surg. 2006;76:740-4.
16. Carnaille B, Oudar C, Pattou F, Combemale F, Rocha J, Proye C. Pancreatitis and primary hyperparathyroidism: forty cases. Aust NZ J Surg. 1998;68:117-19.
17. Shepherd JJ. Hyperparathyroidism presenting as pancreatitis or complicated by postoperative pancreatitis. Aust NZ J Surg. 1996;66:85-7.
18. Sitges-Serra A, de Lecea C AM, Gores PF, Sutherland DE. Pancreatitis and hyperparathyroidism. Br J Surg. 1998;75:158-60.