ISSN 2518-1432 (Online); ISSN 2227-4782 (Print) https://doi.org/10.21856/j-PEP.2022.2.09

FACTORS ASSOCIATED WITH SEVERE HYPERCALCEMIA IN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM*

M. Yazidi, S. Essayeh, I. Oueslati, N. Khessairi, F. Chaker, M. Chihaoui

Department of Endocrinology, University of Tunis El Manar, Faculty of Medicine of Tunis, La Rabta Hospital, Tunis, Tunisia
meriemyazidi@gmail.com

Primary hyperparathyroidism (PHPT) is the most common endocrine pathology after diabetes and hypothyroidism. Its prevalence is 0.3 % in the general population [1, 2]. Due to the increasingly routine dosage of serum calcium, PHPT is nowadays often diagnosed incidentally in the presence of asymptomatic hypercalcemia. In rare cases, however, PHPT may be associated with severe, life-threatening hypercalcemia through predominantly cardiac and neurological complications [3–5]. Few studies have looked at the predictors of severe hypercalcemia in PHPT. The objective of this study was to determine the prevalence of severe hypercalcemia in a hospital cohort of PHPT and to identify its risk factors.

MATERIALS AND METHODS

This is a retrospective study involving the medical records of 123 patients with PHPT collected between January 2000 and December 2019 in the endocrinology department of the Rabta hospital (Tunis – Tunisia). The diagnosis of PHPT was made when serum calcium level was > 2.63 mmol/l associated with high PTH level (> 68 pg/ml). The serum calcium value considered was total serum calcium in the absence of hypoalbuminemia and corrected serum calcium in case of hypoalbuminemia (< 40 g/l). We excluded cases of hypercalcemia with hyperparathyroidism and hypocalciuria and cases of normocalcemic PHPT.

Patients were divided into two groups according to their highest calcium level:

- Severe hypercalcemia (SH) patients including the patients with serum calcium level ≥ 3.25 mmol/l.
- Moderate hypercalcemia (MH) patients including patients with serum calcium level between 2.63 and 3.25 mmol/l.

The two groups of patients were compared according to their socio-demographic, clinical, paraclinical (ECG, laboratory parameters at the time of diagnosis, cervical ultrasound, parathyroid scintigraphy, bone mineral density and renal ultrasound results) and histological (final anatomopathological result in case of surgical treatment) parameters.

Patients with a vitamin D (25-OHD) level < 10 ng/ml were classified as having vitamin D

* The authors guarantee responsibility for everything published in the article, as well as the absence of a conflict of interest and their own financial interest in performing the work and writing an article.

The manuscript was received by the editorial staff 15.01.2022.

deficiency (severe deficiency) and those with 25-OHD between 10 and 30 ng/ml as having a vitamin D insufficiency (moderate deficiency) [6].

The WHO classification was adopted to define osteoporosis and osteopenia [7].

The study was approved by the ethic committee of La Rabta Hospital.

Statistical analysis

Study data were analyzed using SPSS version 23 software. Data were expressed as mean ± standard deviation for quantitative variables and percentages for qualitative variables. Student's t test was used to compare means and Pearson's chi squared and Fisher's exact tests were used to compare proportions. Spearman's correlation was used to assess association between calcium level and clinical and paraclinical quantitative variables. The median value of the distribution was used for the determination of the PTH cutoff (300 pg/ml) and the parathyroid adenoma size cutoff (20 mm). A stepwise binary logistic regression model was applied to determine the variables associated with SH. The significance level was $p \leq 0.05$ for all tests.

RESULTS AND THEIR DISCUSSION

The mean age of the patients was 57.6 ± 12.4 years. The sex ratio (female / male) was 5.15. The prevalence of severe hypercalcemia was 35.8% (n = 44). The hospital incidence of PHPT was 6.47 patients / year. The hospital incidence of severe hypercalcemia associated with PHPT

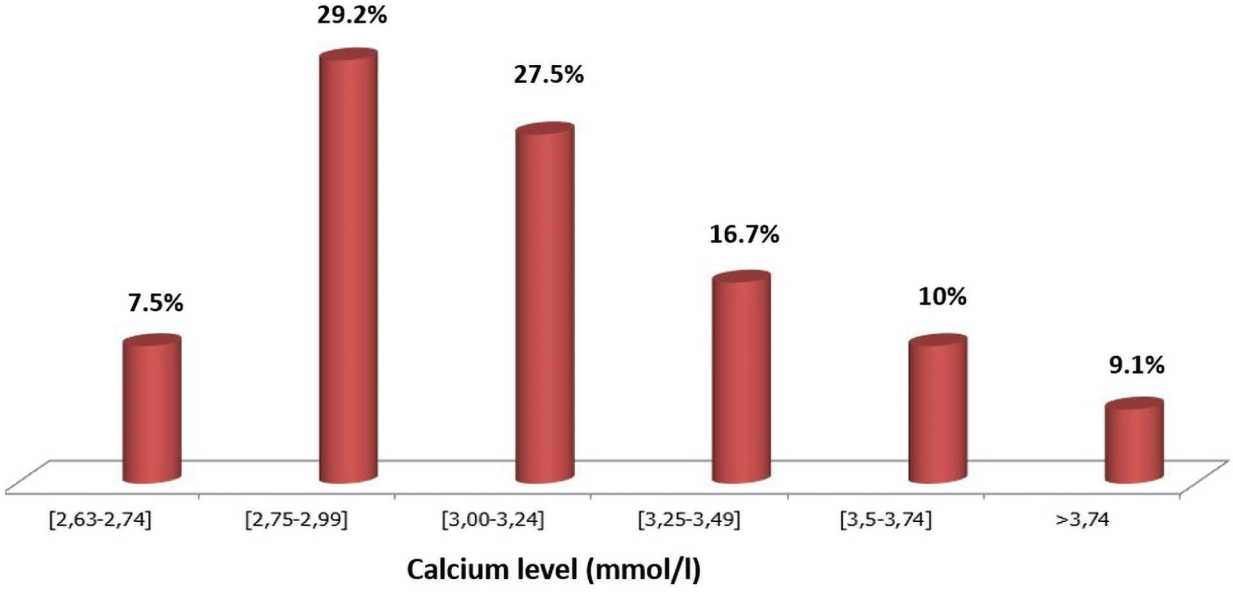

Fig. 1: Distribution of patients according to their calcium level.

Table 1

Clinical and paraclinical parameters correlated with serum calcium level

Parameter	r	p
Heart rate (bpm)	r = 0.189	0.04
QTc (ms)	r = – 0.322	0.008
Phosphoremia (mg/l)	r = – 0.3	0.002
PTH (pg/ml)	r = 0.458	< 0.0001
25-OHD (ng/ml)	r = – 0.286	0.038
Parathyroid adenoma size (mm)	r = 0.407	< 0.0001

Note:
PTH = Parathormone; 25-OHD= vitamin D.

Table 2

Factors associated with severe hypercalcemia in patients with primary hyperparathyroidism after univariate analysis

Parameter	SH group (n = 44)	MH group (n = 79)	p	OR [95 % CI]
Age (years)	58.6 ± 13.1	57.0 ± 12.0	0.49	
Females (%)	79.5	86.1	0.34	0.6 [0.2–1.6]
Confusion (%)	2.3	0	0.35	—
Abdominal pains (%)	11.6	1.3	0.02	10.2 [1.1–90]
Vomiting (%)	9.3	1.3	0.05	8 [0.8–74]
Acute pancreatitis (%)	11.6	0	0.005	—
Heart rate (bpm)	76 ± 12	72 ± 11	0.06	
QTc (ms)	365.11 ± 52.0	384.6 ± 31,9	0.07	
Creatinine clearance (ml/min/1,73 m²)	77.2 ± 33.2	81.7 ± 26.5	0.52	
Phosphoremia (mg/L)	20.4 ± 6.7	23.4 ± 4.6	0.08	
PTH (pg/ml)	819.1 ± 876.0	329.1 ± 268.1	<0.001	
PTH ≥300 (%)	70.5	31.6	<0.001	5.1 [2.3–11.4]
25-OH vit D (ng/ml)	9.5 ± 5.4	17.9 ± 12.5	0.02	
Vitamin D deficiency (%)	70.6	33.3	0.01	4.8 [1.3–16.7]
Renal lithiasis (%)	26.3	22.5	0.65	1.2 [0.4–3.0]
Nephrocalcinosis (%)	7.9	1.4	0.12	6.0 [0.6–59.8]
Osteopenia (%)	21.1	26.6	0.76	0.7 [0.2–2.5]
Osteoporosis (%)	63.2	64.1	0.94	0.9 [0.3–2.7]
Parathyroid adenoma size (mm)	26.0 ± 12.2	17.1 ± 8.7	<0.001	
Parathyroid adenoma size ≥20 mm (%)	52.4	13.3	<0.001	7.1 [2.9–17.5]
Parathyroid carcinoma (%)	15.8	0	0.06	—

Note:
SH = Severe hypercalcemia, MH = Moderate hypercalcemia, PTH = Parathormone, 25-OHD = vitamin D, OR = Odds ratio, CI = confidence interval.

was 2.31 patients / year. Figure 1 shows the distribution of patients according to their serum calcium level.

Heart rate, corrected QT (QTc) interval, phosphoremia, parathyroid adenoma size, PTH and 25OHD levels were correlated with calcium level (Table 1).

The mean calcium level was 3.63 ± 0.4 mmol/l [3.25–5.19] in SH group and 2.94 ± 0.1 mmol/l [2.65–3.21] in MH group ($p < 0.0001$). Table 2 shows the factors associated with severe hypercalcemia after univariate analysis. After multivariate analysis, a PTH level ≥ 300 pg/l and a parathyroid adenoma size ≥ 20 mm were the factors independently associated with severe hypercalcemia (respectively $p = 0.04$, OR [% CI] = 7.7 [1–55] and $p = 0.008$, OR [95 % CI] = 12 [1.9–75]).

In the present study, the prevalence of SH (defined by a calcium level ≥ 3.25 mmol/l) in patients with PHPT was 35.8%. Clinical factors significantly associated with SH were abdominal pain, vomiting and acute pancreatitis. Biological factors associated with SH were higher PTH level and vitamin D deficiency. The parathyroid adenoma size was significantly higher and parathyroid carcinoma was more frequent in patients with SH. After multivariate analysis, the factors independently associated with SH were a parathyroid adenoma size ≥ 20 mm and a PTH level ≥ 300 pg/l (adjusted odds ratios = 12 and 7.7, respectively).

The main limitation of the study is related to its retrospective design. The incidence and prevalence of SH in PHPT is highly variable in the literature. This is mainly related to the

Table 3

Prevalence of severe hypercalcemia in patients with primary hyperparathyroidism in the literature

Study	N*	Cut-off† (mmol/l)	N (Prevalence%)
Lew 2006 [8]	1055	3.75§	43 (4)
Phytayakorn 2008 [9]	292	3.5‡	8 (2.7)
Cannon 2010 [3]	1310	3.5§	88 (6.7)
Starker 2010 [10]	1754	3.4‡	67 (3.8)
Beck 2011 [11]	839	3.5§	34 (4)
Lowell 2017 [12]	183	3‡	29 (15.8)
Gücek Haciyanli 2020 [13]	537	3.5§	24 (4.4)
Notre étude	123	3.25§	44 (35.8)

Note:
* Number of patients included;
† Cut-off defining severe hypercalcemia;
‡ with clinical signs of acute hypercalcemia;
§ with or without clinical signs of acute hypercalcemia.

heterogeneity of the definitions used to characterize SH (Table 3). The prevalence found in our study was higher than the prevalence of most studies, this can be explained by the fact that the cut-off used to define SH in our study is lower than that used by most studies in the literature.

Socio-demographic factors (age and gender), both in our study and in many other studies, were not associated with SH [3, 8–13]. Clinically, the presence of digestive symptoms (abdominal pain, vomiting) was associated with SH. The occurrence of acute pancreatitis was observed only in with SH. Calcium excess promotes the formation of stones in the pancreatic ducts and induces the conversion of trypsinogen into trypsin, which is the active form of the pancreatic enzyme responsible for the self-digestion of the pancreas [9, 14]. Some cardiac signs such as tachycardia and QT segment shortening were also associated with SH. A positive correlation was objectified between the heart rate and the calcium level, and a negative correlation was found between the corrected QT and the calcium level. The relationship between cardiac manifestations and the severity of hypercalcemia is explained by the fact that calcium excess generates faster depolarization of cardiomyocytes, thus promoting the onset of electrical abnormalities including shortening of the QT interval [4]. The frequency of neuropsychic disorders is commonly higher in patients with SH [3, 11].

This was not verified by our study. This may be linked to the cut-off used to define SH, which is lower than that used in many other studies. In addition, neuropsychic signs depend on the age and neuropsychic history of the patients [15].

Biological factors associated with SH in our study were lower serum phosphorus, higher PTH level, and lower vitamin D level. A PTH level higher than 300 pg/ml (approximately 4.5 times the upper limit of normal) was independently associated with SH with an adjusted OR of 7.7. This association makes sense since PTH is directly responsible for the elevation of serum calcium and the decrease of phosphoremia during PHPT. The association with lower vitamin D levels, however, is less clear. Some studies such as ours have found a relationship between the severity of hypercalcemia in PHPT and the frequency of vitamin D deficiency [12, 16]. Several hypotheses have been raised to try to explain this association. One of the most plausible hypotheses would be the increased conversion of 25-OHD to 1,25-dihydroxy-vitamin D. Indeed, PTH stimulates the 1-α-hydroxylase which promotes the conversion of 25-OHD to 1,25-dihydroxy-vitamin D. The

level of 25-OHD will consequently be reduced [17, 18].

We did not find a link between the severity of hypercalcemia and renal or bone complications (renal lithiasis, nephrocalcinosis, chronic renal failure, osteopenia, and osteoporosis). This agrees with several studies in the literature [3, 11, 16, 19, 20]. In fact, renal and bone complications of PHPT are more correlated with the duration and the chronicity of the disease than with the severity of hypercalcemia [19, 21]. Bone complications are also related to other factors such as age, gender, and vitamin D status [22].

The size of the parathyroid adenoma was positively correlated with the calcium level. A size higher than 20 mm was independently associated with the severity of hypercalcemia with an adjusted OR equal to 12. The correlation between the severity of biological abnormalities and the size of the parathyroid adenoma is controversial [23, 24]. It is common to find a relation between the severity of hypercalcemia and the size of the lesion [24].

Histologically, cases of parathyroid carcinoma have only been noted in patients with SH. Most studies, like ours, agree on a higher prevalence of parathyroid carcinoma in patients with SH [3, 8–10, 13, 25]. Compared to parathyroid adenoma, parathyroid carcinoma appears to be larger with an average diameter of 3.4 cm [26]. It tends to be more frequently present when hypercalcemia is higher than 3 mmol/l with a PTH level higher than three times the upper limit of normal [26–29].

CONCLUSION

Factors independently associated with SH in PHPT were a PTH level higher than 300 pg/ml and a parathyroid adenoma size higher than 20 mm. Cardiac and digestive complications seem to be more frequent when PHPT is associated with SH. Vitamin D deficiency also appears to be more common in these forms of PHPT, justifying its systematic screening and supplementation in case of deficiency. Finally, it is important to fear parathyroid carcinoma and to speed up surgical management when PHPT is associated with SH.

REFERENCES

1. Fraser WD. *Lancet* 2009;374: 145-158.
2. Pepe J, Cipriani C, Pilotto R, et al. *J Endocrinol Invest* 2011;34(7): S40-S44.
3. Cannon J, Lew JI, Solórzano CC. *Surgery* 2010;148(4): 807-812.
4. Guidon C. Hypercalcémies sévères: Encycl Med Chir. (Anesthesie-Reanimation), *Paris*, 2016: 11p.
5. Shazia A, Gayatri K, Devin S. *Am J Med* 2015;128(3): 239-245.
6. Hanley DA, Cranney A, Jones G, et al. *Can Med Assoc J* 2010;182(12): 610-618.
7. World Health Organisation. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis, *available at: https://apps.who.int/iris/handle/10665/39142*
8. Lew JI, Soloranzo CC, Irvin GL, et al. 3rd. *Arch Surg* 2006;141(7): 696-699.
9. Phitayakorn R, Machenry CR. *J Am Coll Surg* 2008; 206(3): 1106-1115.
10. Starker LF, Björklund P, Theoharis C, et al. *World J Surg* 2010;35(2): 331-335.
11. Beck W, Lew JI, Solórzano CC. *J Surg Res* 2011;171(2): 404-408.
12. Lowell AJ, Bushman NM, Wang X, et al. *J Surg Res* 2017;217: 252-257.
13. Gücek Haciyanli S, Acar N, Ogür E, et al. *Ann R Coll Surg Engl* 2020;102(5): 363-368.
14. Arya AK, Bhadada SK, Mukhjee S. *Indian J Med Res* 2018;148(6): 721-727.
15. Minisola S, Romagnoli E, Carnevale V, Scillitani A. Acute management of hypercalcemia. In: Bilezikian JP, dir. The Parathyroids: basic and clinical concepts, *New York,* 2014: 617-629.
16. Yan H, Calcatera N, Moo-Young TA, et al. *Am J Surg* 2019;217(3): 437-440.
17. Davies M, Heys SE, Selby PL. *J Clin Endocrinol Metab* 1997;82: 209-212.
18. Malabanan A, Veroniks IE, Holick MF. *Lancet* 1998; 351: 805-806.
19. Boone D, Politz D, Lopez J, et al. *Surgery* 2017;161(1): 98-106.
20. Amaral LM, Queiroz DC, Marques TF, et al. *J Osteoporos* 2012;2012: 1-5.
21. Walker MD, Nickolas T, Kepley A. *J Clin Endocrinol Metab* 2014;99(5): 1885-1892.
22. Cormier C, Souberbielle JC, Kahan A. *Rev Med Interne* 2004;25(5): S560-S567.

23. Randhawa PS, Mace AD, Nouraei SA. *Clin Otolaryngol* 2007;32: 179-184.

24. Hamidi S, Aslani A, Nakhjavani M. *ANZ J Surg* 2006; 76: 882-885.

25. Gasparri G, Camandona M, Mullineris B, et al. *Ann Ital Chir* 2004;75: 321-324.

26. Erovic BM, Goldstein DP, Kim D, et al. *Head Neck* 2013; 35(1): 35-39.

27. Betea D, Potorac I, Beckers A. *Ann Endocrinol* 2015;76: 169-177.

28. Schulte KM, Talat N. *Nat Rev Endocrinol* 2012;8: 612-622.

29. Do Cao C, Aubert S, Trinel C, et al. *Ann Endocrinol* 2015;76: 165-168.

FACTORS ASSOCIATED WITH SEVERE HYPERCALCEMIA IN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM

M. Yazidi, S. Essayeh, I. Oueslati, N. Khessairi, F. Chaker, M. Chihaoui

Department of Endocrinology, University of Tunis El Manar, Faculty of Medicine of Tunis, La Rabta Hospital, Tunis, Tunisia
meriemyazidi@gmail.com

Objectives: To determine the factors associated with severe hypercalcemia (SH) in primary hyperparathyroidism (PHPT).

Methods: This is a retrospective study involving the medical records of 123 patients with PHPT collected over a period of 20 years. The patients were subdivided into two groups according to their highest calcium level: ≥ 3.25 mmol/l (SH) or < 3.25 mmol/l (Moderate hypercalcemia). The two groups were compared by univariate and multivariate analysis according to their socio-demographic, clinical and paraclinical parameters.

Results: The prevalence of SH was 35.8 %. Clinical factors associated with SH were abdominal pain (p = 0.02), vomiting (p = 0.05), and acute pancreatitis (p = 0.005). Biological factors associated with SH were higher PTH level (p = 0.001) and vitamin D deficiency (p = 0.01). The parathyroid adenoma size was significantly higher and parathyroid carcinoma was more frequent in the SH group (p = 0.001 and p = 0.06, respectively). After multivariate analysis, the factors independently associated with SH were a parathyroid adenoma size ≥ 20 mm and a PTH level ≥ 300 pg /ml (adjusted odds ratios = 12 and 7.7 respectively).

Conclusion: In patients with PHPT, a PTH level ≥ 300 pg/ml and a parathyroid adenoma size ≥ 20 mm are the main predictors of the onset of SH. Acute pancreatitis and parathyroid carcinoma appear to be more common in these forms of PHPT, requiring prompt surgical management after medical preparation.

Keywords: primary hyperparathyroidism, severe hypercalcemia, parathyroid hormone, parathyroid carcinoma, surgery.

ФАКТОРИ, АСОЦІЙОВАНІ З ТЯЖКОЮ ГІПЕРКАЛЬЦІЄМІЄЮ У ПАЦІЄНТІВ З ПЕРВИННИМ ГІПЕРПАРАТИРЕОЗОМ

М. Язіді, С. Ессайє, І. Уеслаті, Н. Хессайрі, Ф. Чакер, М. Чіхауї

Кафедра ендокринології Туніського університету Ель-Манар, Медичний факультет Тунісу, лікарня Ла Рабта, м. Туніс, Туніс
meriemyazidi@gmail.com

Мета: визначити фактори, пов'язані з тяжкою гіперкальціємією (ТГК) при первинному гіперпаратиреозі (ПГПТ).

Матеріали та методи. Проведено ретроспективне дослідження, яке включає медичні записи 123 пацієнтів із ПГПТ, зібрані протягом 20 років. Пацієнти були розподілені на дві групи за найвищим рівнем кальцію: ≥ 3,25 ммоль/л (ТГК) або < 3,25 ммоль/л (помірна гіперкальціємія). Дві групи порівнювалися за допомогою однофакторного та багатофакторного аналізу за їх соціально-демографічними, клінічними та параклінічними параметрами.

Результати. Поширеність ТГК становила 35,8%. Клінічними факторами, пов'язаними з ТГК, були біль у животі (p = 0,02), блювота (p = 0,05) та гострий панкреатит (p = 0,005). Біологічними факторами, пов'язаними з ТГК, були вищий рівень паратгормону (p = 0,001) та дефіцит вітаміну D (p = 0,01). Розмір аденоми паращитовидної залози був значно вищим, а карцинома паращитовидної залози частіше зустрічалася в групі ТГК (p = 0,001 та p = 0,06 відповідно). Після багатофакторного аналізу факторами, незалежно пов'язаними з ТГК, були розмір аденоми паращитовидної залози ≥ 20 мм і рівень паратгормону ≥ 300 пг/мл (кориговані співвідношення шансів = 12 і 7,7 відповідно).

Висновок. У пацієнтів із ПГПТ рівень паратгормону ≥ 300 пг/мл та розмір аденоми паращитовидної залози ≥ 20 мм є основними предикторами початку тяжкої гіперкальціємії. Гострий панкреатит і карцинома паращитовидної залози частіше зустрічаються при цих формах ПГПТ, що вимагають швидкого хірургічного лікування після медичної підготовки.

Ключові слова: первинний гіперпаратиреоз, тяжка гіперкальціємія, паратгормон, карцинома паращитовидної залози, хірургічне втручання.