Endokrynologia Polska
Tom/Volume 63; Numer Number 6/2012
ISSN 0423–104X

Hypercalcaemic crisis due to primary hyperparathyroidism — a systematic literature review and case report

Przełom hiperkalcemiczny z powodu pierwotnej nadczynności przytarczyc — przegląd piśmiennictwa i opis przypadku

Angela Gurrado, Giuseppe Piccinni, Germana Lissidini, Pasquale Di Fronzo, Francesco Vittore, Mario Testini

Department of Biomedical Sciences and Human Oncology, Unit of Endocrine, Digestive, and Emergency Surgery, Aldo Moro University Medical School, Bari, Italy

Abstract

Hypercalcaemic crisis is an uncommon and potentially life-threatening manifestation of primary hyperparathyroidism, and it is associated with rapid deterioration of the central nervous system, and cardiac, gastrointestinal, and renal function. We present the case of a 76 year-old man in a sudden coma due to hypercalcaemic crisis as a first manifestation of primary hyperparathyroidism. At first, the patient was treated conservatively, his mental status gradually improved in the next three days. On the ninth day after the initiation of therapy, a minimally invasive radio-guided parathyroidectomy was performed. Histologically, the tumour consisted of densely arranged chief cells immunohistochemically positive for PTH antigens, suggesting adenoma. Calcaemia level and PTH were normalised in the immediate postoperative period. A systematic review was performed by consulting PubMed MEDLINE for publications from 1958 to 2011. This review found a total of 499 reported cases of hypercalcaemic crisis due to primary hyperparathyroidism. Manifestations are neurological alterations, and cardiac, renal and gastrointestinal dysfunctions associated with markedly elevated serum calcium and parathyroid hormone levels. The most frequent histology is the parathyroid adenoma. In untreated cases, mortality is 100%. Despite advances in its management, the mortality rate is still 93.5% in patients treated only conservatively. Medical therapy followed by expeditious parathyroidectomy should be considered as the treatment of choice for patients affected by hypercalcaemic crisis due to a primary hyperparathyroidism. **(Endokrynol Pol 2012; 63 (6): 494–502)**

Key words: *hypercalcaemic crisis, hyperparathyroidism, hypercalcaemia, parathyroid*

Streszczenie

Przełom hiperkalcemiczny jest rzadkim choć potencjalnie zagrażającym życiu objawem pierwotnej nadczynności przytarczyc i jest skojarzony z gwałtownym pogorszeniem funkcji ośrodkowego układu nerwowego, serca, przewodu pokarmowego i funkcji nerek.
W pracy zaprezentowano przypadek 76-letniego mężczyzny, u którego pierwszym objawem pierwotnej nadczynności przytarczyc był przełom hiperkalemiczny w postaci nagłej śpiączki. Na początku pacjent był leczony zachowawczo i jego stan psychiczny zaczął ulegać stopniowej poprawie w ciągu pierwszych 3 dni. Dziewiątego dnia terapii wykonano u niego mini inwazyjny zabieg usunięcia przytarczyc pod kontrolą RTG. Histologicznie guz składał się z gęsto ułożonych dużych komórek pozytywnych badaniem imunohistologiczno-chemicznym dla antygenów PTH, sugerując gruczolak. Stężenie wapnia i PTH znormalizowano w bezpośrednim okresie pooperacyjnym.
Dokonano systematycznego przeglądu publikacji PubMed MEDLINE w latach 1958–2011. Przegląd zawiera łącznie 499 odnotowanych przypadków przełomu hiperkalcemicznego jako objawu pierwotnej nadczynności przytarczyc. Przejawy to zmiany neurologiczne, dysfunkcja nerek, przewodu pokarmowego i serca związanych ze znacznie podwyższonym stężeniem wapnia i parathormonu w surowicy. W badaniu histologicznym najczęściej diagnozowany jest gruczolak przytarczycowy. W przypadkach nieleczonych odnotowuje się 100-procentową śmiertelność. Mimo postępów w leczeniu, przy terapii tylko zachowawczej, śmiertelność jest nadal wysoka — 93,5%. Leczenie zachowawcze plus szybkie usuniecie przytarczyc powinny być uważane za leczenie z wyboru u pacjentów dotkniętych przełomem hiperkalcemicznym z powodu pierwotnej nadczynności przytarczyc. **(Endokrynol Pol 2012; 63 (6): 494–502)**

Słowa kluczowe: *przełom hiperkalcemiczny, pierwotna nadczynność przytarczyc, hiperkalcemia, przytarczyca, ostra nadczynność przytarczyc*

Introduction

Serum calcium levels greater than 15 mg/dL (3.75 mmol/L) associated with rapid deterioration of the central nervous system, cardiac, gastrointestinal, and renal function depict the so-called hypercalcaemic crisis. This is an uncommon manifestation of severe calcium intoxication, requiring prompt diagnosis and rapid treatment in order to avoid a lethal course. Indeed, unless treated, the mortality rate is basically 100% [1, 2].

Hypercalcaemia, when compensated, is caused more frequently by malignancy, primary hyperparathyroidism (PHPT) and vitamin D-induced hypercalcaemia, and less frequently by thyrotoxicosis, drug-induced condition (e.g. thiazide diuretics, lithium, oestrogens and antioestrogens, androgens, vitamin A), immobilisation, tuberculosis, rabdomyolysis, sarcoidosis, milk-alkali syndrome, kidney disease and familial hypocalciuric

Angela Gurrado M.D., Ph.D., Unit of Endocrine, Digestive, and Emergency Surgery, Aldo Moro University Medical School, Policlinico, Piazza G. Cesare, 11–70124 Bari, Italy, tel.: +39 80 559 28 82, fax: +39 80 559 28 82, e-mail: angelagurrado@libero.it

hypercalcaemia. However, the cause of hypercalcaemic crisis is PHPT in the majority of cases [2–5].

Generally, PHPT is found incidentally with no apparent clinical manifestations, via simple laboratory tests. The simultaneous occurrence of hypercalcaemia and elevated (or non-suppressed) PTH level in fact proves the parathyroid origin of the disease. A patient rarely shows a severe hypercalcaemic crisis as his or her first manifestation of PHPT.

We present the case of a severe and sudden hypercalcaemic crisis as a first presentation of PHPT secondary to a parathyroid adenoma.

Case report

A 76 year-old man was admitted as an emergency to the Department of Neurology due to a sudden syncopal episode that lapsed into coma. Anamnesis revealed that the patient was in good general health, and did not take vitamin supplements, lithium or thiazide diuretics. He had had polyuria of two weeks' duration prior to admission. Endocrinologic family history was uneventful.

On physical examination, the patient presented severe dehydration, but his blood pressure was 170/90 mm Hg and ECG revealed a sinus rhythm with normal QT intervals. Laboratory tests on admission showed severe renal insufficiency with elevated S-urea (202 mg/dL, normal = 7-40 mg/dL) and S-creatinine levels (3.1 mg/dL, normal = 0.80–1.30 mg/dL), hypercalcaemia (22.5 mg/dL, normal = 8.5–10.1 mg/dL), hypophosphataemia (0.55 mg/dL, normal = 2.5–4.50 mg/dL), an increase in intact-PTH (1,109 pg/mL, normal = 6.4–52 pg/mL) and in 1,25-dihydroxycholecalciferol levels (230.7 pg/mL, normal = 15.9–55.6 pg/mL). Urine biochemistry indicated elevated 24-hour urine calcium excretion (511 mg/24 h, normal range = 42–353 mg/24 h), phosphate clearance (711 mL/min, normal range = 400–1300 mg/24 h) and proteinuria (725 mg/24 h, normal range = 0–150 mg/24 h). Thyroid tests were within normal limits; tumour markers and blood tests for metabolic abnormalities were negative; pancreatic enzymes were normal.

A cerebral CT scan showed no pathological findings and a diffuse slow activity was revealed by the electroencephalogram.

At first, the patient was treated conservatively with aggressive intravenous isotonic chloride infusion, furosemide in intravenous dosages from 20–40 mg/d once intravascular volume was restored, and 300 mg/d of intravenous disodium clodronate tetrahydrate. The mental status of the patient gradually improved over the next three days and, on the seventh day after the initiation of therapy, the calcaemia was 11.7 mg/dL and the renal function normalised.

On abdomen ultrasound there was no suspicion of kidney stones or nephrocalcinosis and there were no signs of pancreatitis. Neck ultrasound demonstrated the non-pathological thyroid and an encapsulated hypoechoic mass of 1.9 × 1.2 cm in the lower portion of the left thyroid lobe. Tc-99m sodium pertechnetate/Tc-99m-sestamibi parathyroid dual-phase scintigraphy with subtraction image technique revealed the mass to be a left inferior parathyroid adenoma.

A minimally invasive radio-guided parathyroidectomy was performed on day 9. One hour before surgery, 50 MBq of Tc-99m — sestamibi was injected intravenously; in the operating suite, the gamma probe (MR-100, 11C, Pol.hi.tech) was used to recognise the following: *in vivo* localisation of the cutaneous projection of the adenoma; *ex vivo* uptake of the 2.5 cm excised adenoma and, lastly to confirm removal of the pathologic parathyroid, on the 'background' operated area. An apparently normal biopsy of the right inferior parathyroid was performed. Intraoperative PTH was reduced by more than 50% compared to the normal preoperative level.

Histologically, the tumour consisted of densely arranged chief cells with no indication of malignancy and immunohistochemically positive for PTH (DakoCytomation; dilution 1:100; mouse) antigens, suggesting adenoma. The gland biopsy was normal.

Calcaemia level and PTH were normal in the immediate postoperative period (9 mg/dL and 11 pg/mL, respectively) and one, six and 12 months after surgery (9.2–9–8.8 mg/dL, and 10.5–19–15 pg/mL, respectively).

Recovery was uneventful and the patient was discharged 72 hours after the operation.

Discussion

In 1923, Dawson et al. [6] reported the autopsy of a patient who died following a syncopal attack, where the main features were a parathyroid adenoma, generalised osteitis fibrosa and metastatic calcifications. This was probably the first case of parathyroid crisis, although the authors did not recognise it as such.

In 1925, the physiologic effects of PTH were studied in dogs by Collip, [7] with repeated injections of the hormone, causing serum calcium increase, vomiting, diarrhoea, atony, coma and death.

In 1932, Lowenberg [8] reported similar evidence due to excessive amounts of parathyroid extract for the treatment of purpura in a 5 year-old boy. However, Wank [9] first described the case of a hyperparathyroid crisis due to double parathyroid adenomas treated with parathyroidectomy, which pursued an acute and fatal course 19 days after the operation.

This pathological condition, also called *parathyrotoxicosis, acute hyperparathyroidism*, *parathyroid storm*, and *parathyroid intoxication*, or *poisoning*, is a rare, life-threatening complication due to a severe increase of serum calcium level. There is no standard definition for this syndrome [2, 3, 10–24]. Some authors have considered patients presenting slight disturbances in mental status, lethargy or muscle weakness and serum calcium levels around 14 to 16 mg/dL [2, 3, 12–21, 23, 24], as being affected by hypercalcaemic crisis, whereas others included only cases of deep coma [10, 22].

Because hypercalcaemic crisis is predominantly parathyrotoxic crisis [2–5], PHPT must be confirmed or excluded. The reported incidence of hypercalcaemic crisis due to PHPT is variable, ranging from 1.6% to 6% of patients treated surgically [10, 11, 18, 25], and this range includes several defining criteria. Moreover, the frequency of the syndrome is modified by the introduction of PTH radioimmunoassay [26, 27] and of intact-PTH immunoradiometric assay [28, 29].

A systematic review was performed by consulting PubMed MEDLINE for publications from 1958 to 2011 limited to the English language only and matching the terms of hypercalcaemic crisis/hyperparathyroid crisis/parathyroid intoxication/parathyroid storm/parathyrotoxicosis/acute hyperparathyroidism/parathyroid poisoning AND primary hyperparathyroidism (Table I).

This review found a total of 499 cases, the majority of which were women (165 M and 300 F, of whom 20were pregnant), while in the remaining 34/499 patients, the sex was not reported; the mean age was 43.94 years calculated on 424/499 patients, because the age of 75/499 was not reported. The reported serum calcium average was 18 mg/dl (in 460/499 patients).

The table shows that the PTH value was not reported before 1978 because hormone assay dates from 1963 [26]. Therefore, PTH level was reported in 310/499 cases; it was always elevated.

The commonest symptoms of hypercalcaemic crisis are severe nephrolithiasis, constipation, unrelenting peptic ulcer disease and osteoporosis. Patients infrequently present cardiac arrhythmias and neurocognitive derangements, but, in the literature, this symptom is often considered the discriminant factor for definition of the disease [2, 3, 10–24].

Mental status was reported in 217/499 cases in the literature; it was normal in 20.2% of patients only, while it was pathological in 173/217 (79.8%). In spite of 50/173 patients (29%) being in a coma, there were different neurological alterations in 123/173 (71%) cases.

There is often no clear reason for the sudden evolution of PHPT to a state of crisis, but in some cases, this syndrome is probably precipitated by bacterial or viral infection [114], trauma, recent surgery [60, 115], and the use of a calcium antagonist [116]. However, hypercalcaemic crisis may also occur in the absence of any precipitating factor [18].

Surgery was performed in 415/499 patients, while treatment with hydration and diuretics was only reserved in 31/499; in 53/499 cases, the type of treatment (surgery or conservative) was not reported.

There were discordant opinions regarding the timing of surgery. Some authors suggest an urgent parathyroidectomy [3, 13, 14, 18, 23, 24, 68], while others propose medical management [2, 5].

Standard medical care consists of intravenous isotonic sodium chloride solution in order to obtain the intravascular volume expansion, and IV loop diuretics to induce calciuresis [2, 3,12, 13, 15, 38, 43]. Hypocalcaemic drugs, such as bisphosphonates, have also been employed as adjuncts to reduce serum calcium levels, inhibiting osteoclast function and serving as an effective bridge to elective parathyroidectomy [18].

However, medical therapy followed by expeditious parathyroidectomy is considered by the majority of authors [3, 13, 14, 17, 18, 23, 24, 68] to be the treatment of choice for patients affected by hypercalcaemic crisis due to PHPT, and this is usually our therapeutic approach, as in this reported case.

Histology was reported in 352/499 cases: histological examination reveals that the majority of specimens were adenoma (85%); the others were multiglandular disease (9%) and carcinoma (6%).

In the literature review, the outcome was reported in 369/499 cases. Despite the advances in the management of hypercalcaemic crisis, the mortality rate is 15.5% (57/369 patients). The table shows that the mortality was 6.7% (28/415 reported cases) in surgically treated patients and 93.5% (29/31 reported cases) in conservatively treated patients. This data is very important in order to confirm the rationale of medical therapy followed by quick parathyroidectomy.

Hypercalcaemic crisis remains a rare and potentially lethal clinical manifestation of PHPT and it should be considered as a dramatic complication of severe hypercalcaemia. Multidisciplinary management should be performed in order to obtain hydration and diuresis and to surgically remove the cause of manifestation. Because hypercalcaemic crisis may be the first manifestation of PHPT, as in the reported case, we suggest that the assay of PTH and imaging of the neck should be primarily considered in the diagnostic approach of a patient affected by this biochemical abnormality, in association with prompt supportive medical therapy.

Acknowledgment

The authors thank Prof. Malcolm Clark for assistance in the preparation of the English manuscript.

Table I. *Hypercalcemic crisis due to primary hyperparathyroidism: literature review*
Tabela I. *Kryzys hiperglikemiczny z powodu pierwotnej nadczynności przytarczyc — przegląd literatury*

Author	n. cases	Age*	Gender	Serum calcium level†	PTH‡	Neurological alterations/ Coma	Surgery	Hystology	Outcome
Jabiev et al. [12], 2011	14	n.r.	n.r.	n.r.	n.r.	n.r.	yes	n.r.	S
Hajsadeghi et al. [30], 2011	1	60	M	20.5	1160	n.a.	n.r.	n.r.	S
Walczyk et al. [31], 2011	2	9.5	F	13.4	n.r.	no	yes	A	S
Beck et al. [13], 2011	34	57	9 M; 25 F	15.8	719	8 n.a.; 26 n.r.	yes	n.r.	n.r.
Baumann et al. [32], 2011	1	23	F; p	12.3	890	no	yes	A	S
Starker et al. [14], 2011	67	57	40 F; 27 M	13.9	392.5	20 n.a.; 47 n.r.	yes	3 C; 57 A; 7 H	S
Cannon et al. [17], 2010	88	57	32 M; 56 F	15.6	782	16 n.a.; 72 n.r.	41 yes; 47 n.r.	4 C; 84 n.r.	n.r.
Rock et al. [15], 2010	1	60	M	18.6	1743	c	yes	C	S
Nilsson et al. [33], 2010	2	31.5	F; p	n.r.	394.5	n.r.	yes	A	S
McMullen et al. [16], 2010	7	n.r.	F; p	12.1	178	n.r.	yes	A	S
Van den Hauwe et al. [34], 2009	1	50	M	23.6	> 1900	c	yes	A	S
Taskapan et al. [35], 2008	1	77	F	13.8	25.1	no	no	n.r.	S
Phitayakorn et al. [18], 2008	8	44.6	F; 3/8 p	16.2	691.7	3 c; 5 n.r.	yes	7 A; 1 C	S
Shani et al. [36], 2008	1	31	F; p	14	> 1,000	c	yes	A	S
Huang et al. [37], 2007	1	58	F	16.2	1048	no	yes	A	S
Ntaios et al. [38], 2007	1	61	F	17.6	525.8	c	yes	A	S
Valdivielso et al. [39], 2006	1	63	M	25	7280	c	no	C	D
Lew et al. [3], 2006	43	60	27 F; 16 M	17.1	n.r.	15 n.a.; 1 c; 27 n.r.	yes	36 A; 5 H; 1 C; 1 n.r.	42 S; 1 D
Makita et al. [40], 2006	1	64	M	16.7	470	no	yes	A	S
Wani et al. [41], 2005	1	76	F	18.3	1472	no	yes	A	S
Zuberi et al. [42], 2005	1	40	F	14.1	2500	c	yes	A	S
Gasparri et al. [43], 2004	35	54	21 M; 14 F	17.1	593.4	20 n.a.; 15 no	yes	24 A; 8 H; 3 C	34 S; 1 D
Altun et al. [44], 2004	1	63	M	16.3	540	no	yes	A	S
Cherry et al. [19], 2002	1	19	F; p	14	555	no	yes	A	S
Kuzucu et al. [45], 2002	1	50	F	17.6	2500	no	yes	A	S
Dionisi et al. [46], 2002	1	35	M	15.7	707	n.r.	yes	A	D

Ziegler et al. [2], 2001	1	42	F	23.6	n.r.	n.a.	yes	A	D
Tołłoczko et al. [47], 2000	2	n.r.	n.r.	n.r.	n.r.	n.r.	yes	A	D
Gurbuz et al. [48], 1996	1	83	F	18.7	1401	no	yes	A	S
Sarfati et al. [49], 1994	4	n.r.	n.r.	n.r.	n.r.	n.r.	yes	A	n.r.
Ohrvall et al. [20], 1994	6	79	n.r.	15.3	n.r.	n.r.	yes	3 A; 3 H	S
Minisola et al. [50], 1993	1	56	M	21.2	1315	c	yes	A	S
Pezzi et al. [51], 1993	1	65	F	16.6	19000	c	yes	A	S
Martinez et al. [52], 1992	1	80	F	16.8	1600	c	yes	A	S
Kelly et al. [25], 1991	2	n.r.	F; p	n.r.	n.r.	n.r.	yes	1 A; 1 C	S
Clark et al. [53], 1991	1	84	F	n.r.	n.r.	n.r.	yes	n.r.	D
Gunn et al. [54], 1989	4	62.2	3 F; 1 M	n.r.	500.7	n.r.	3 yes; 1 no	A	3 S; 1 D
Chadli et al. [55], 1988	1	44	F	12.4	n.r.	c	yes	A	S
McHenry et al. [56], 1988	1	23	M	14	2605	c	yes	A	S
Matthias et al. [57], 1987	1	34	F	20	n.r.	c	yes	A	D
Vernava et al. [58], 1987	2	51	1 M; 1 F	21	219	c	no	A	D
Keeling et al. [59], 1987	1	35	F	30.4	n.r.	c	no	A	D
Evans et al. [60], 1987	1	43	M	16.9	n.r.	no	yes	A	S
Sherwood et al. [21], 1986	3	61.6	1 F; 2 M	12.7	2140	1 n.a.; 2 n.r.	yes	A	S
Higashi et al. [61], 1986	2	n.r.	n.r.	n.r.	n.r.	n.r.	no	n.r.	1 S; 1 D
Corlew et al. [62], 1985	1	70	M	n.r.	n.r.	n.r.	no	n.r.	D
Wang et al. [63], 1985	4	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Piccione et al. [64], 1984	1	32	F	15	n.r.	n.a.	yes	A	S
Hans et al. [65], 1984	1	73	F	13.9	2822	c	yes	A	S
Calandra et al. [66], 1983	2	66	M	15.6	n.r.	c	yes	A	S
Thomason et al. [67], 1981	1	44	F; p	12.9	n.r.	no	yes	A	S
Kelly et al. [68], 1981	6	56	3 M; 3 F	17.6	870	3 c; 3 n.a.	yes	A	S
Maselly et al. [10], 1981	10	n.r.	3 M; 7 F	16.5	n.r.	1 c; 3 n.a.; 6 no	yes	9 A; 1 H	S
Clark et al. [69], 1981	1	41	F; p	19.4	3659	c	yes	A	S
Payne et al. [70], 1980	1	34	M	15.9	171	c	yes	A	S
Bayat-Mokhtari et al. [22], 1980	1	71	F	19.5	1424	c	yes	A	S
Wang et al. [23], 1979	14	52	8 M; 6 F	17.6	n.r.	6 c; 2 n.a.; 6 no	12 yes; 2 no	12 A; 1 C; 1 H	12 S; 2 D

Thomas et al. [71], 1979	1	70	F	16.4	n.r.	n.a.	yes	n.r.	S
Schweitzer et al. [24], 1978	29	n.r.	23 F; 6 M	13.6	689	1 c; 28 n.a.	28 yes; 1 no	25 A; 2 C; 1 H; 1 n.r.	27 S; 2 D
Block et al. [72], 1975	1	74	n.r.	n.r.	n.r.	n.r.	yes	n.r.	D
Dorey et al. [73], 1975	1	26	F; p	14.8	n.r.	n.r.	yes	A	S
Burcharth et al. [74], 1973	4	51.2	3 F; 1 M	19.8	n.r.	n.r.	yes	A	2 S; 2 D
Bergqvist et al. [75], 1972	1	10	M	19.6	n.r.	n.r.	yes	A	S
Miller et al. [76], 1972	1	43	F	18	n.r.	n.r.	yes	A	S
Boquist et al. [77], 1971	1	65	F	15.4	n.r.	c	yes	A	D
Houck et al. [78], 1971	1	47	F	13.9	n.r.	n.r.	yes	A	S
Yeager et al. [79], 1971	6	55.5	F	18.6	n.r.	n.r.	2 no; 4 yes	5 A; 1 C	3 S; 3 D
Gardner et al. [80], 1969	1	49	M	31.2	n.r.	c	yes	n.r.	S
Kelly et al. [81], 1968	1	58	F	16	n.r.	no	yes	A	S
MacLeod et al. [82], 1967	1	76	F	19.6	n.r.	no	yes	A	D
Bartlett et al. [83], 1967	1	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	A	S
Clunie et al. [84], 1967	4	47.7	3 F; 1 M	19.1	n.r.	1 c; 3 n.r.	1 no; 3 yes	3 A; 1 C	2 S; 2 D
Flink et al. [85], 1966	4	49.7	F	19.8	n.r.	c	yes	A	3 S; 1 D
Anglem et al. [86], 1966	1	59	M	21	n.r.	n.r.	yes	A	D
Kleppel et al. [87], 1965	1	43	M	20	n.r.	c	yes	A	D
Payne et al. [88], 1965	2	47	F	20.9	n.r.	1 c; 1 no	yes	A	S
Chodack et al. [89], 1965	2	62	F	19.5	n.r.	n.r.	1 yes; 1 no	A	1 S; 1 D
Kutner et al. [90], 1965	2	52	F	20.4	n.r.	n.r.	yes	A	S
Schenker et al. [91], 1965	1	30	F	n.r.	n.r.	n.r.	no	H	D
Henley et al. [92], 1964	5	56.4	3 F; 2 M	19	n.r.	n.r.	3 no; 2 yes	A	2 S; 3 D
Pringle et al. [93], 1964	2	50	M	19.5	n.r.	n.r.	yes	A	D
Lemann et al. [4], 1964	4	57.7	F	19.4	n.r.	3 c; 1 n.a.	3 yes; 1 no	A	2 S; 2 D
Wilson et al. [94], 1964	3	57	2 F; 1 M	18.8	n.r.	n.r.	yes	2 A; 1 H	1 S; 2 D
Mansberger et al. [95], 1964	1	61	F	20	n.r.	n.r.	yes	A	S
Naik et al. [96], 1963	1	45	M	19.5	n.r.	n.r.	no	C	D
Smith et al. [97], 1963	3	50.3	2 F; 1 M	18.9	n.r.	1 c; 1 n.a.; 1 no	yes	1 A; 2 H	2 S; 1 D
Templeton et al. [98], 1962	1	61	M	19.8	n.r.	n.r.	yes	H	S
Klein et al. [99], 1962	1	67	F	17.4	n.r.	n.r.	no	A	D

Gershberg et al. [100], 1962	1	77	M	19.8	n.r.	n.r.	no	A	D
Veenema et al. [101], 1961	2	63	1 M; 1 F	18.7	n.r.	n.r.	1 no; 1 yes	A	D
Reinfrank et al. [102], 1961	1	13	F	22.4	n.r.	n.r.	yes	A	S
Nelson et al. [103], 1961	1	49	M	17.8	n.r.	n.r.	yes	A	S
Fink et al. [104], 1961	1	60	M	20	n.r.	n.a.	yes	A	D
Bottino et al. [105], 1961	1	48	M	20	n.r.	n.r.	no	A	D
Spinner et al. [106], 1960	1	62	M	18.4	n.r.	n.r.	yes	A	S
Silvestrini et al. [107], 1960	2	41.5	F	17.5	n.r.	n.r.	no	A	D
Murphy et al. [108], 1960	1	51	M	17	n.r.	n.r.	yes	A	S
Gassman et al. [109], 1960	1	50	F	17.8	n.r.	n.r.	no	A	D
Derbyshire et al. [110], 1960	1	61	M	26	n.r.	n.r.	yes	A	D
Carlson et al. [111], 1960	1	53	F	16.9	n.r.	n.r.	no	H	D
Atsmon et al. [112], 1960	1	49	F	18.6	n.r.	n.r.	yes	A	S
Horowitz et al. [113], 1958	1	30	F	17.6	n.r.	c	no	A	D

*years; †mg/dL; ‡pg/mL; n.r. — not reported; p — pregnant; n.a. — neurological alterations; c — coma; A — adenoma; C — carcinoma; H — multiglandular disease; S — survival; D — death

References

1. Huang JJ, Sung JM, Wu TJ et al. Parathyroid storm: report of two cases. J Formos Med Assoc 1992; 91: S255–259.
2. Ziegler R. Hypercalcemic crisis. J Am Soc Nephrol 2001; 12: S3–9.
3. Lew JI, Solorzano CC, Irvin GL. 3rd. Long-term results of parathyroidectomy for hypercalcemic crisis. Arch Surg 2006; 141: 696–699.
4. Lemann J Jr, Donatelli AA. Calcium intoxication due to primary hyperparathyroidism: a medical and surgical emergency. Ann Intern Med 1964; 60: 447–461.
5. Mazzaferri EL, O'Dorisio TM, LoBuglio AF. Treatment of hypercalcemia associated with malignancy. Semin Oncol 1978; 5: 141–153.
6. Dawson JW, Struthers JW. Generalized Osteitis fibrosa with parathyroid tumor and metastatic calcification. Edinburgh Med J 1923; 30: 421.
7. Collip JP, Clarke EP, Scott JW. Effect of parathyroid hormone on normal animals. J Biol Chem 1925; 63: 439.
8. Lowenberg H, Ginsburg TM. Acute hypercalcemia: report of a case. JAMA 1932; 99: 1166.
9. Wanke R. Reitrag zur stoffwechsel untersuchung der osteodystrophia fibrosa. Deutsch Z Chir 1930; 228: 210.
10. Maselly MJ, Lawrence AM, Brooks M et al. Hyperparathyroid crisis: successful treatment of ten comatose patients. Surgery 1981; 90: 741–746.
11. Wang CA, Guyton SW. Hyperparathyroid crisis: clinical and pathologic studies of 14 patients. Ann Surg 1979; 190: 782–790.
12. Jabiev AA, Lew JI, Garb JL, Sanchez YM, Solorzano CC. Primary hyperparathyroidism in the underinsured: A study of 493 patients. Surgery 2012; 151: 471–476.
13. Beck W, Lew JI, Solórzano CC. Hypercalcemic crisis in the era of targeted parathyroidectomy. J Surg Res 2011; 171: 404–408.
14. Starker LF, Björklund P, Theoharis C et al. Clinical and histopathological characteristics of hyperparathyroidism-induced hypercalcemic crisis. World J Surg 2011; 35: 331–335.
15. Rock K, Fattah N, O'Malley D, McDermott E. The management of acute parathyroid crisis secondary to parathyroid carcinoma: a case report. J Med Case Reports 2010; 4: 28.
16. McMullen TP, Learoyd DL, Williams DC et al. Hyperparathyroidism in pregnancy: options for localization and surgical therapy. World J Surg 2010; 34: 1811–1816.
17. Cannon J, Lew JI, Solórzano CC. Parathyroidectomy for hypercalcemic crisis: 40 years' experience and long-term outcomes. Surgery 2010; 148: 807–812.
18. Phitayakorn R, McHenry CR. Hyperparathyroid crisis: use of bisphosphonates as bridge to parathyroidectomy. J Am Coll Surg 2008; 206: 1106–1115.
19. Cherry TA, Kauffman RP, Myles TD. Primary hyperpararathyrodism, hypercalcemic crisis and subsequent seizures occurring during pregnancy: a case report. J Matern Fetal Neonatal Med 2002; 12: 349–352.
20. Ohrvall U, Akerström G, Ljunghall S et al. Surgery for sporadic primary hyperparathyroidism in the elderly. World J Surg 1994; 18: 612–618.
21. Sherwood JK, Garcia M, Ackroyd FW et al. Hyperparathyroid crisis reviewed: a role for parenteral cimetidine? Am Surg 1986; 52: 320–332.
22. Bayat-Mokhtari F, Palmieri GM, Moinuddin M et al. Parathyroid storm. Arch Intern Med 1980; 140: 1092–1095.
23. Wang CA, Guyton SW. Hyperparathyroid crisis: clinical and pathologic studies of 14 patients. Ann Surg 1979; 190: 782–790.
24. Schweitzer VG, Thompson NW, Harness JK et al. Management of severe hypercalcemia caused by primary hyperparathyroidism. Arch Surg 1978; 113: 373–381.
25. Kelly TR. Primary hyperparathyroidism during pregnancy. Surgery 1991; 110: 1028–1033.
26. Berson SA, Yalow RS, Aurbach GD et al. Immunoassay of bovine and human parathyroid hormone. PNAS 1963; 49: 613–617.
27. Berson SA, Yalow RS. Immunochemical heterogeneity of parathyroid hormone in plasma. J Clin Endocrinol Metab 1968; 28: 1037–1047.
28. Nussbaum SR, Potts JT. Advances in immunoassays for PTH: clinical applications to skeletal disorders of bone and mineral metabolism. In: Bilezikian JP, Marcus R, Levine MA, (eds.) The parathyroids. New York: Raven Press 1994: 157–170.
29. Nussbaum SR, Zahradnik RJ, Lavigne JR et al. Highly sensitive two-site immunoradiometric assay of parathyrin and its clinical utility in evaluating patients with hypercalcaemia. Clin Chem 1987; 33: 1364–1367.
30. Hajsadeghi S, Chitsazan M, Miresmail SJ. A rare electrocardiographic manifestation of a rare form of multiple electrolyte disturbances: hyperparathyroid crisis. Acta Med Iran 2011; 49: 824–827.
31. Walczyk A, Szalecki M, Kowalska A. Primary hyperparathyroidism: a rare endocrinopathy in children. Two case reports. Endokrynol Pol 2011; 62: 346–350.
32. Baumann K, Weichert J, Krokowski M et al. Coexistent parathyroid adenoma and thyroid papillary carcinoma in pregnancy. Arch Gynecol Obstet 2011; 284: 91–94.
33. Nilsson IL, Adner N, Reihnér E et al. Primary hyperparathyroidism in pregnancy: a diagnostic and therapeutic challenge. J Women Health (Larchmt) 2010; 19: 1117–1121.

34. Van den Hauwe K, Oeyen SG, Schrijvers BF et al. A 50-year-old man with severe hypercalcemia: a case report. Acta Clin Belg 2009; 64: 442–446.
35. Taskapan H, Vieth R, Oreopoulos DG. Unusually prolonged vitamin D intoxication after discontinuation of vitamin D: possible role of primary hyperparathyroidism. Int Urol Nephrol 2008; 40: 801–805.
36. Shani H, Sivan E, Cassif E et al. Maternal hypercalcemia as a possible cause of unexplained fetal polydramnion: a case series. Am J Obstet Gynecol 2008; 199: 410.ei-5.
37. Huang SC, Wu VC, Chou G et al. Benign parathyroid adenoma presenting with unusual parathyroid crisis, anemia and myelofibrosis. J Formos Med Assoc 2007; 106: S13–16.
38. Ntaios G, Savopoulos C, Chatzinikolaou A et al. Parathyroid crisis as first manifestation of primary hyperparathyroidism. Eur J Intern Med 2007; 18: 551–552.
39. Valdivielso P, Lopez-Sanchez J, Garrido A et al. Metastatic calcifications and severe hypercalcemia in a patient with parathyroid carcinoma. J Endocrinol Invest 2006; 29: 641–644.
40. Makita N, Iiri T, Sato J et al. An instructive case suggesting cyclical primary hyperparathyroidism. Endocr J 2006; 53: 311–316.
41. Wani S, Hao Z. Atypicl cystic adenoma of the parathyroid gland: case report and review of literature. Endocr Pract 2005; 11: 389–393.
42. Zuberi LM, Talati JJ, Jabbar A et al. Parathyroid apoplexy manifesting as fever of unknown origin. Endocr Pract 2005; 11: 180–183.
43. Gasparri G, Camandona M, Mullineris B et al. Acute hyperparathyroidism: our experience with 36 cases. Ann Ital Chir 2004; 75: 321–324.
44. Altun H, Ozdemir A, Hamaloglu E et al. Hyperfunctioning parathyroid cyst: a case report. Acta Chir Belg 2004; 104: 234–236.
45. Kuzucu A, Sojsal O, Savli H. Giant mediastinal parathyroid adenoma presenting with a hyperparathyroid crisis and leading to postoperative hungry bone sindrome. Eur J Surg 2002; 168: 747–749.
46. Dionisi S, Minisola S, Pepe J et al. Concurrent parathyroid adenomas and carcinoma in the setting of MEN type 1: presentation as hypercalcemic crisis. Mayo Clin Proc 2002; 77: 866–869.
47. Tołłoczko T, Chudziński W, Nawrot I. Surgery for primary hyperparathyroidism. Przegl Lek 2000; 57: 101–103.
48. Gurbuz AT, Peetz ME. Giant mediastinal parathyroid cyst: an unusual cause of hypercalcemic crisis — case report and review of the literature. Surgery 1996; 120: 795–800.
49. Sarfati E, Dubost C. Posterior mediastinal parathyroid adenoma and hyperparathyroid crisis. Surgery 1994; 115: 661–662.
50. Minisola S, Romagnoli E, Scarnecchia L et al. Parathyroid storm: immediate recognition and pathophysiological considerations. Bone 1993; 14: 703–706.
51. Pezzi CM, Sirico-Kelly F, Maxwell RJ et al. Hyperparathyroid crisis and posterior mediastinal parathyroid adenoma: a case for preoperative localization. Surgery 1993; 113: 590–593.
52. Martínez E, Domingo P. Herpes zoster-induced acute hyperparathyroid crisis. Clin Infect Dis 1992; 14: 1270–1271.
53. Clark OH, Wilkes W, Siperstein AE et al. Diagnosis and management of asymptomatic hyperparathyroidism: safety, efficacy, and deficiencies in our knowledge. J Bone Miner Res 1991; 6: S135–142.
54. Gunn IR, Halkett JM. Rapid and accurate diagnosis of acute hyperparathyroid crisis. Lancet 1989; 2: 618–619.
55. Chadli MC, Chaieb L, Jemni L et al. Bigeminal arrhythmia associated with hyperparathyroid crisis. CMAJ 1988; 138: 1115–1116.
56. McHenry C, Walsh M, Jarosz H et al. Resection of parathyroid tumor in the aorticopulmonary window without prior neck exploration. Surgery 1988; 104: 1090–1094.
57. Matthias GS, Helliwell TR, Williams A. Postpartum hyperparathyroid crisis. Case report. Br J Obstet Gynaecol 1987; 94: 807–810.
58. Vernava AM, O'Neal LW, Palermo V. Lethal hyperparathyroid crisis: hazards of phosphate administration. Surgery 1987; 102: 941–948.
59. Keeling CA, Abrahamson MJ, Harloe DG. Fatal hyperparathyroid crisis. Postgrad Med J 1987; 63: 111–112.
60. Evans RA. Aminohydroxypropylidene diphosphonate treatment of hypercalcemic crisis due to primary hyperparathyroidism. Aust N Z J Med 1987; 17: 58–59.
61. Higashi K, Morita M, Tajiri J et al. Rapid diagnosis of parathyroid storm. CMAJ 1986; 135: 971.
62. Corlew DS, Bryda SL, Bradley EL, DiGirolamo M. Observations on the course of untreated primary hyperparathyroidism. Surgery 1985; 98: 1064–1071.
63. Wang CA. Surgical management of primary hyperparathyroidism. Curr Probl Surg 1985; 22: 1–50.
64. Piccione W Jr, Selenkow HA, Cady B. Management problems in coexisting parathyroid crisis and florid thyrotoxicosis. Surgery 1984; 96: 1009–1014.
65. Hans SS, Lee PT. Hypercalcemic crisis due to unsuspected parathyroid adenoma in a patient with advanced breast carcinoma. Am Surg 1984; 50: 230–232.
66. Calandra DB, Shah KH, Prinz RA et al. Parathyroid cysts: a report of eleven cases including two associated with hyperparathyroid crisis. Surgery 1983 ec; 94: 887–892.
67. Thomason JL, Sampson MB, Farb HF et al. Pregnancy complicated by concurrent primary hyperparathyroidism and pancreatitis. Obstet Gynecol 1981; 57: 34S–6S.
68. Kelly TR, Zarconi J. Primary hyperparathyroidism: hyperparathyroid crisis. Am J Surg 1981; 142: 539–542.
69. Clark D, Seeds JW, Cefalo RC. Hyperparathyroid crisis and pregnancy. Am J Obstet Gynecol 1981; 140: 840–842.
70. Payne JE Jr, Tanenberg RJ. Hyperparathyroid crisis and acute necrotizing pancreatitis presenting as diabetic ketoacidosis. Am J Surg 1980; 140: 698–703.
71. Thomas B, Schelstraete E, Rolly G. Emergency surgery for acute hyperparathyroidism: anesthetic aspects. Acta Anaesthesiol Belg 1979; 30: 153–161.
72. Block MA, Xavier A, Brush BE. Management of primary hyperparathyroidism in the elderly. J Am Geriatr Soc 1975; 23: 385–389.
73. Dorey LG, Gell JW. Primary hyperparathyroidism during the third trimester of pregnancy. Obstet Gynecol 1975; 45: 469–472.
74. Burcharth F, Castberg T, Vibe-Hansen H. Primary hyperparathyroidism. Acta Chir Scand Supp 1973; 433: 169–177.
75. Bergqvist E, Sjöberg HE, Hjern B et al. Calcitonin in the treatment of hypercalcaemic crisis. Acta Med Scand 1972; 192: 385–389.
76. Miller EM. Hypercalcemic crisis in hyperparathyroidism. Report of a case. J Med Soc N J 1972; 69: 131–134.
77. Boquist L, Bergdahl L, Andersson A. Parathyroid adenoma complicated by acute hyperparathyroidism: report of a case with particular regard to ultrastructural findings. Ann Surg 1971; 173: 593–603.
78. Houck WS Jr, Parker WF Jr, Moore RE Jr. Parathyroid crisis: a surgical emergency. J S C Med Assoc 1971; 67: 169–171.
79. Yeager RM, Krementz ET. Acute hyperparathyroidism. South Med J 1971; 64: 797–803.
80. Gardner RJ, Koppel DM. Hyperparathyroid crisis. Arch Surg 1969; 98: 674–676.
81. Kelly TR, Falor WH. Hyperparathyroid crisis associated with pancreatitis. Ann Surg 1968; 168: 917–920.
82. MacLeod WA, Holloway CK. Hyperparathyroid crisis. A collective review. Ann Surg 1967; 166: 1012–1015.
83. Bartlett WC. Acute hyperparathyroid crisis. Am J Surg 1967; 114: 796–799.
84. Clunie GJ, Gunn A, Robson JS. Hyperparathyroid crisis. Br J Surg 1967; 54: 538–541.
85. Flink EB, Desper PC, Jones JE. Primary hyperparathyroidism causing hypercalcemic crisis and acute pancreatitis. Minn Med 1966; 49: 734–744.
86. Anglem TJ. Acute hyperparathyroidism: a surgical emergency. Surg Clin North Am 1966; 46: 727–746.
87. Kleppel NH, Goldstein MH, Leveen HH. Hypercalcemic crisis and pancreatitis in primary hyperparathyroidism. JAMA 1965; 192: 916–918.
88. Payne RL Jr, Fitchett CW. Hyperparathyroid crisis: survey of the literature and a report of two additional cases. Ann Surg 1965; 161: 737–747.
89. Chodack P, Attie JN, Groder MG. Hypercalcemic crisis coincidental with hemorrhage in parathyroid adenoma. Arch Intern Med 1965; 116: 416–423.
90. Kutner FR, Morton JH. Parathyroid crisis. Arch Surg 1965; 91: 71.
91. Schenker JG, Kallner B. F et al. postpartum hyperarathyroid crisis due to primary chief cell hyperplasia of parathyroids. Report of a case. Obstet Gynecol 1965; 25: 705–709.
92. Henley RB. Management of the parathyroid crisis. Am J Surg 1964; 108: 183–190.
93. Pringle A, Smith EK. Renal vein thrombosis in acute hyperparathyroidism. Br Med J 1964; 2: 675–676.
94. Wilson RE, Bernhard WF, Polet H et al. Hyperparathyroidism: the problem of acute parathyroid intoxication. Ann Surg 1964; 159: 79–93.
95. Mansberger AR Jr, Lovice H, Mclaughlin JS. Intermittent acute hypercalcemic crisis. Am Surg 1964; 30: 167–176.
96. Naik BK, Sarma RN, Gopalrao V et al. Acute hyperparathyroidism. Report of a fatal case, with ECG findings. Arch Intern Med 1963; 111: 729–733.
97. Smith LC, Bradshaw HH, Holleman IL Jr. Hyperparathyroid crisis: a surgical emergency. Am Surg 1963; 29: 761–767.
98. Templeton TB. Parathyroid crisis successfully treated by surgery, report of a case. N C Med J 1962; 23: 22–24.
99. Klein L, Albertsen K, Curtiss PH Jr. Urinary hyperparathyroidism: a study of three cases with and without bone lesions. Metabolism 1962; 1: 1023–1027.
100. Gershberg H, Jonas S, Stiff DP. Hyperparathyroidism with uremia in a 77-year-old man. JAMA 1962; 182: 136–139.
101. Veenema RJ, Longo FW, Fish GW. Functioning parathyroid tumors: clinical pathology and diagnostic criteria. J Urol 1961; 85: 183–188.
102. Reinfrank RF, Edwards TL Jr. Parathyroid crisis in a child. JAMA 1961; 178: 468–471.
103. Nelson AR, Cantrell JR. Acute parathormone poisoning complicating parathyroid adenoma. Arch Surg 1961; 83: 1–10.
104. Fink WJ, Finfrock JD. Fatal hyperparathyroid crisis associated with pancreatitis. Am Surg 1961; 27: 424–430.

105. Bottino C. On a case of embolic occlusion of the central artery of the retina in the course of acute hyperparathyroidism ("parathyroid poisoning"). Ann Ottalmol Clin Ocul 1961; 87: 583–588.
106. Spinner S. Primary hyperparathyroidism with acute parathyroid hormone intoxication. Postgrad Med 1960; 28: 368.
107. Silvestrini F, Faglia G, Bregani P et al. On 2 cases of hyperparathyroid crises with fatal outcome. Folia Endocrinol Mens Incretologia Incretoterapia 1960; 13: 217–230.
108. Murphy TR, Remine WH, Burbank MK. Hyperparathyroidism: report of a case in which parathyroid adenoma presented primarily with profound muscular weakness. Proc Staff Meet Mayo Clin 1960; 35: 629–634.
109. Gassman R, Hass HE. Acute hyperparathyroidism. Schweiz Med Wschr 1960; 90: 67.
110. Derbyshire RC, Angle RM. Acute hyperparathyroidism: case report. Am Surg 1960; 26: 166–170.
111. Carlson KP, Bates HB, Boyce WH. Death due to parathyroid crisis. J Urol 1960; 84: 219–222.
112. Atsmon A, Frank M, Nathan P et al. Recurrent acute hyperparathyroidism with severe gastrointestinal manifestations. Gastroenterology 1960; 39: 83.
113. Horowitz W, Berenbaum AA. Primary hyperparathyroidism due to a parathyroid adenoma: antemortem diagnosis with termination in possible acute parathyroid hormone intoxication. Ann Intern Med 1958; 49: 181–189.
114. Martinez E, Domingo P. Herpes zoster-induced acute hyperparathyroid crisis. Clin Infect Dis 1992; 14: 1270–1271.
115. Norton JA, Aurbach GD, Marx SJ, Doppman JL. Surgical management of hyperparathyroidism. In: DeGroot LJ (ed.). Endocrinology. 2nd ed. Vol 2. Philadelphia: WB Saunders, 1989: 1013–1031.
116. Samani NJ. Nifedipine and hypercalcemia of primary hyperparathyroidism. Lancet 1991; 337: 372.