

# Acute Hyperparathyroidism: our experience with 36 cases



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## Introduction

Acute hyperparathyroidism is a condition which has been known as acute parathyroid intoxication, parathyroid crisis, parathormone intoxication and calcium intoxication, since 1926 when Collip injecting parathyroid hormone into dogs, observed vomiting, diarrhoea and atony with an increase of serum calcium level to above 20 mg/dl.

In 1932 Lowenberg and Ginsberg reported a case of acute hypercalcemia due to excessive amounts of parathyroid extract given in the treatment of purpura in a 5-year-old boy. In the same year, Dawson and Struthers reported the first case of hyperparathyroidism which pursued an acute and rapidly fatal course.

In 1964, Payne and Fitchett reviewed the literature and noted only 68 cases of hyperparathyroid crisis and added 2 cases, while in 1987 Fitzpatrick and Bilezikian, in another retrospective analysis of the literature, pointed out 43 cases and 5 cases were added. In 1993 Bondeson found 10% incidence on 514 neck explorations and Wang 14% in parathyroid carcinoma (1, 2, 3, 4, 5, 6).

A review of recent literature and a retrospective analysis of our patients was made in order to focus on the characteristic features of HPT correlated syndrome.

## Riassunto

### L'IPERTIROIDISMO ACUTO

**Obiettivi:** L'IPT acuto è una condizione patologica grave e rappresenta un'emergenza medico-chirurgica: viene sotto-lineata la difficoltà nel porre una diagnosi precisa. Scopo del nostro lavoro è quello di rivedere i più attuali schemi di trattamento e le condizioni che favoriscono la crisi ipercalcemica acuta.

**Materiali e metodi:** È stato eseguito uno studio retrospettivo su 1321 pazienti (638 HPT primari, 683 secondari o terziari) operati dal 1975 al Dicembre 2002 per Iperparatiroidismo primitivo, secondario e terziario.

**Risultati:** Su 638 casi di iperparatiroidismo primitivo, le ipercalcemie gravi (calcemia superiore ai 15 mg/dl) sono comparse in 35 pazienti. Confrontando questi casi con la popolazione iperparatiroidica operata ma con una calcemia inferiore ai 15 mg/dl, si è notato come la presenza di un doppio adenoma o di un carcinoma sia più frequente rispetto ai controlli, come pure l'aspetto cistico della lesione. Il peso dell'adenoma od i valori abnormemente alti di PTH sono strettamente correlati con la comparsa di questa sindrome. Anche le complicazioni ne riflettono la gravità: si passa infatti da una mortalità inferiore allo 0.1% ad una mortalità del 2,8%.

**Conclusioni:** Queste sue caratteristiche rappresentano uno stimolo in più per un intervento precoce ben prima che si manifestino quegli squilibri idroelettrolitici legati all'ipercalcemia che possono condurre ad un quadro clinico di gravissima compromissione generale.

Nell'IPT secondario e terziario (pazienti operati) questa sindrome rappresenta una assoluta rarità: essa è comparsa in un solo caso di IPT secondario e mai nel terziario su 683 pazienti operati dal 1975 al Dicembre 2002.

Parole chiave: Iperparatiroidismo; IPT, paratormone; PTH.

## Abstract

**Objectives:** acute hypercalcemia is a serious condition and represents a physician-surgical emergency: the difficulty in setting a precise diagnosis is due to several possibilities that can cause the condition. It is our purpose to critically evaluate the most actual schemes of treatment and the conditions that could favour the appearance of a hypercalcemic acute crisis.

**Materials and Methods:** *A retrospective study was performed considering 1321 patients (638 primary HPT, 683 secondary or tertiary HPT) operated from 1975 to December 2002 for Primary, Secondary and Tertiary HPT. Results: it should be noticed that out of 638 cases of Primary HPT this syndrome was present in 35 patients (Ca higher than 15 mg/dl): if you compare these cases with the hyperparathyroid population with calcium less than 15 mg/dl it is possible to observe that a double adenoma or a carcinoma were more frequently found in acute HPT, as the cystic appearance of the lesion. The weight of the adenoma and the PTH assay are strictly correlated with the appearance of this syndrome. The mortality rate is also higher (2.8% to 0.1%) than in the hyperparathyroid patient who underwent parathyroidectomy without hypercalcemic crisis.*

**Conclusion:** *These characteristics suggest that an early operation is mandatory in the patients in whom such a possibility could be expected, before serious involvement of the cardiovascular, renal or neuromuscular system.*

*We can point out the rarity of this syndrome in Secondary and Tertiary HPT: just one case in Secondary out of 683 patients operated on from 1975 until December 2002.*

**Key words:** Hyperparathyroidism: HPT, parathormone: PTH.

## Materials and Methods

Since 1975 to December 2002, in the III Department of General and Oesophageal Surgery of the University of Turin, Italy, 1321 patients (638 primary HPT, 683 secondary or tertiary HPT), underwent a neck exploration. 36 patients had a serum calcium level higher than 15 mg/dl (35 with primary HPT and only 1 with secondary HPT).

When considering the 603 cases of primary HPT with a serum calcium level lower than 15 mg/dl, 456 were females, 147 males; the mean age was 56; the mean PTH level and serum calcium were respectively 244 pg/ml and 11.9 mg/dl. The renal system was involved in 60.8% of the cases, skeletal in 59.8%, gastrointestinal in 6.9% and nervous in 17.2%. A MEN syndrome was observed in 16 cases (2.6%). A single adenoma occurred in 77.9% of the cases, a double adenoma in 11.1%, hyperplasia in 9.2%, a carcinoma in 1.8% and a cystic adenoma in 1.3%. The mean weight of the removed glands was 2119 mg. The operative mortality was 0.1%, due to a case of cardiac failure; complete recovery was obtained in 98.1% of the cases. (Table I)

In the group of patients with serum calcium level higher than 15 mg/dl, males were more numerous than females (21 males, 14 females); the mean age was 54; mean PTH level and serum calcium were respectively 593.4 pg/ml and 17.1 mg/dl. A renal involvement was observed in 71.4% of the cases, skeletal in 48.5%, gastrointestinal in 2.8%, and nervous in 57.1%. A MEN syndrome was never seen. A single adenoma occurred in 68.7% of the cases; a double adenoma in 17.1%;

Tab. I – 603 CASES OF PRIMARY HPT WITH CALCIUM <15 MG/DL OPERATED FROM 1975 UNTIL DECEMBER 2002

Males	147
Females	456
Average age (years)	56
Mean PTH	244 pg/ml
Mean calcium	11,9 mg/dl
Renal syndrome	60.8%
Bone syndrome	59.8%
Gastrointestinal syndrome	6.9%
Neurological syndrome	17.2%
MEN	2.6%
Single adenoma	77.9%
Double adenoma	11.1%
Hyperplasia	9.2%
Carcinoma	1.8%
Cystic adenoma	1.3%
Complete recovery	98.1%
Operative mortality	0.1%
Mean parathyroid weight	2119 mg

Tab. II – 35 CASES OF PRIMARY HPT WITH CALCIUM >15 MG/DL OPERATED FROM 1975 UNTIL DECEMBER 2002

Males	21
Females	14
Average age (years)	54
Mean PTH	593.4 pg/ml
Mean calcium	17.1 mg/dl
Renal syndrome	71.4%
Bone syndrome	48.5%
Gastrointestinal syndrome	2.8%
Neurological syndrome	57.1%
MEN	0%
Single adenoma	68.7%
Double adenoma	17.1%
Hyperplasia	5.7%
Carcinoma	8.5%
Cystic adenoma	5.7%
Complete recovery	94%
Operative mortality	2.8%
Mean parathyroid weight	4947 mg

hyperplasia in 5.7%; a carcinoma in 8.5%, and a cystic adenoma in 5.7%. The mean weight of the removed glands was 4947 mg. The operative mortality was 2.8% and a complete recovery was obtained only in 94% of the cases. (Table II)

## Results and discussion

The criteria for the inclusion of patients in the group of acute Hyperparathyroidism was the serum calcium level above 15 mg/dl. In this situation, often, progressi-

ve changes in a patient's general condition occur rapidly, especially when acute symptoms involve gastrointestinal, cardiovascular or central nervous systems. Differential diagnosis in the case of severe hypercalcemia is difficult but HPT should be suspected considering the PTH level (often twenty time the normal level). Bone metastases from mammary, prostate, lung; neoplasia of the lung, necks kidney, pancreas and ovary that produced a PTH-related protein that interferes with the PTH cell receptor without a feed-back mechanism; the multiple myeloma with cytochine production that stimulates the bone osteoclastic reabsorption, are all conditions to be kept in mind. Nowadays the differential diagnosis is easier due to rapid PTH assay. The presence of hypercalcemia with an elevated PTH is a sign of acute HPT. An elevated serum chlorum level (the PTH reduces the bicarbonates reabsorption in the distal renal tubule and increases the chlorum reabsorption with a light acidosis), a high alkaline itases (elevated in 10% of primary HPT but in 75% of patients with hyperparathyroid crisis), the presence of a twenty-four hour urinary calcium level more than 280 mg in males and 200 mg in females, all these features could be warning signs for acute HPT. The patient's history is an important element to be pointed out because the majority of patients with acute hypercalcemia are known as having a HPT; the presence of a breast, prostate, kidney or lung tumour, a multiple myeloma, is another point that could orient the surgeon to the correct diagnosis (Table III).

It has been suggested that certain factors, such as a minor operation or anaesthesia, head trauma or undue manipulation of parathyroid adenoma, a high milk and alkali intake for a long period, a prolonged bed rest (increases the mobilization of calcium from skeleton), recurrent high temperature with dehydration, they can all trigger an acute HPT.

The symptoms are well known: anorexia, polyuria, nausea and vomiting are the principal ones. A delay in the diagnosis and treatment could lead to an important dehydration with a worsening of the metabolic status. Cardiovascular, renal and central nervous systems malfunction occur with progression to stupor, coma and exitus.

The treatment must be urgent, keeping in mind that it is the same whatever is the initial cause. Principal basis of therapy are rehydration, than forced renal calcium

excretion decreasing bone reabsorption, but only when volume repletion has been achieved. After this treatment it is possible, normally a few days later, to treat the cause; if HPT is the diagnosis an operation has to be performed.

Rehydration can be obtained by infusion of physiologic solution (500 ml intravenous) followed by 4-6 litres in the next 24 hours. In fact anorexia, vomiting and polyuria cause an important dehydration with a renal damage and a decreased calcium excretion.

The necessity to check the patient's reaction after hydration, looking closely at the central venous pressure, is of vital importance. Diuretics like Furos can be given (40-80 mg every 2-4 hours). The main risk of this therapy is cardiovascular decompensation, hypophosphataemia, hypokalaemia, hypomagnesaemia.

In the first 48 hours, hospitalisation in an intensive care unit is important, constantly monitoring central venous pressure, ECG and saturation; furthermore diuresis must be checked every hour and serum electrolytes every 4-6 hours.

If necessary, after the critical phase, Bisphosphonates and Calcitonin can be given. Bisphosphonates do not act directly on the kidneys, but they have an effective inhibiting action on osteoclasts. Calcitonin has the same effect and a moderate analgesic and calciuric action. Other drugs like Mithramycin, Gallium nitrate, Glucocorticoids and intravenous phosphate have been used with poor results and some important side effects. Peritoneal dialysis or haemodialysis can be useful in the treatment of these patients in order to rapidly remove calcium. (7, 8, 9)

Our patient's data have been compared with Fitzpatrick and Bilezikian's reviewed cases: the mean age was similar, but we observed more males than females, renal involvement was more frequent in our cases (71.4% versus 69%), but the skeletal involvement was not (48.5 versus 53%). The mean serum calcium and PTH level are similar for both reviewed cases (Table IV).

We also observed a high percentage of neuromuscular involvement (57.1%).

Comparing the normal HPT population, in our experience, single adenomas are less frequent in patients with a serum calcium level higher than 15 mg/ dl (77.9% vs. 68.7%); double adenomas are more frequent (11.1% vs.

Tab. III – DIFFERENTIAL DIAGNOSIS IN ACUTE HYPERCALCEMIA

– Bone osteolytic metastasis (breast, prostate, lung)
– PTH related protein (some solid tumor of the lung, neck, kidney, pancreas, ovary).
– Multiple myeloma
– Increase intake of milk
– A long term treatment using Thiazides
– Primary HPT

Tab. IV – 48 CASES OF ACUTE PRIMARY HPT REPORTED BY FITZPATRICK AND BILEZIKIAN (1974-1981)

Female male ratio	1.1:1
Average age (years)	55
Mean PTH	10 times higher
Mean calcium	17.5 mg/dl
Renal syndrome	69%
Bone syndrome	53%

17.1%), as well as carcinomas (1.8% vs. 5.7%) and cystic adenomas (1.3% vs. 8%). (10, 11, 12) Hyperplasia is rarely seen (9.2% vs. 5.7%). The mean weight of removed glands was 2119 mg versus 4947 in acute HPT.

Size, weight, a cystic aspect, as well as a suspect diagnosis of carcinoma are important features to be correlated with this syndrome and could be an important factor to influence an emergency treatment.

It should be noted that in secondary and tertiary HPT, even if the weight of the removed parathyroid tissue reach a high level (mean weight 3426 mg in secondary HPT, 2635 in tertiary HPT), hypercalcemic crisis are unusual and just one case in secondary HPT was observed.

Immediate and long-term results reflect the gravity of this particular form of HPT: operative mortality rises from 0.1% to 2.8% (acute pancreatitis), recurrences from 1.9% to 6%.

## Conclusions

The acute hypercalcemia is an important medical and metabolic emergency that could appear during the natural course of HPT. Unfortunately, clear, predictive symptoms do not exist, but the size of the adenoma, the cystic aspect, the suspicion of a carcinoma and an abnormal high PTH could represent a significant sign of alarm and an indication for prompt surgical treatment. It must be pointed out that double adenomas and carcinomas appear more frequently in our series, so the risk of persistence of HPT is high if the surgeon does not explore the neck bilaterally removing all pathological tissue.

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