



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

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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 hiperkalcemiczny 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 immunohistologiczno-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 usunięcie 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, przytarczycyca, 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, rhabdomyolysis, sarcoidosis, milk-alkali syndrome, kidney disease and familial hypocalcaemic



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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/^{99m}Tc-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 20 were 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.

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Table 1. *Hypercalcemic crisis due to primary hyperparathyroidism: literature review*
 Tabela 1. *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
Toffozzco 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.	1 no; 1 yes		A	D
Reinfrank et al. [102], 1961	1	13	F	22.4	n.r.	yes		A	S
Nelson et al. [103], 1961	1	49	M	17.8	n.r.	yes		A	S
Fink et al. [104], 1961	1	60	M	20	n.a.	yes		A	D
Bottino et al. [105], 1961	1	48	M	20	n.r.	no		A	D
Spinner et al. [106], 1960	1	62	M	18.4	n.r.	yes		A	S
Silvestrini et al. [107], 1960	2	41.5	F	17.5	n.r.	no		A	D
Murphy et al. [108], 1960	1	51	M	17	n.r.	yes		A	S
Gassman et al. [109], 1960	1	50	F	17.8	n.r.	no		A	D
Derbyshire et al. [110], 1960	1	61	M	26	n.r.	yes		A	D
Carlson et al. [111], 1960	1	53	F	16.9	n.r.	no		H	D
Atsmon et al. [112], 1960	1	49	F	18.6	n.r.	yes		A	S
Horowitz et al. [113], 1958	1	30	F	17.6	n.r.	no		A	D

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

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