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Hyperparathyroidism with Normal Albumin-Corrected Total Calcium in Patients with Multiple Endocrine Neoplasia Type 1

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In the largest reported family of patients with multiple endocrine neoplasia type 1 (MEN 1), hyperparathyroidism was expressed at first screening in 33 patients by elevation of ionized calcium (IC) (30 cases) or parathyroid hormone (three cases) without elevation of albumin-corrected total calcium (ACTC). Three of these 33 patients have shown a progressive rise in IC and later an elevation of ACTC. However, the age distribution suggests that in others the level of IC may remain stable at a minimally elevated level throughout life with ACTC remaining normal except for transient rises at the times of intercurrent illness or surgical operation. Even when ACTC is normal preoperatively, patients with an elevation of IC require radical subtotal parathyroidectomy or total parathyroidectomy and forearm implantation to restore IC to a normal level. Institutions that rely on ACTC as a screening test for hyperparathyroidism in MEN 1 will miss the diagnosis in nearly half of patients under the age of 30. The greatest deficiency in using ACTC occurs in the follow-up of patients who have undergone parathyroidectomy for MEN 1. Only three of 11 recurrences were evidenced by this measurement. (Henry Ford Hosp Med J 1992;40:186-90)

A number of authors (1-3) have suggested that ionized serum calcium (IC) may be a better discriminant or elevated more consistently than albumin-corrected total serum calcium (ACTC) or parathyroid hormone (PTH) in patients with hyperparathyroidism. Previous studies have dealt predominantly with middle-aged or elderly patients. The presence of a large family (4) of patients in Tasmania with multiple endocrine neoplasia type 1 (MEN 1) has made it possible to screen large numbers of young patients who are at 50% risk of developing parathyroid hyperplasia, as well as more elderly patients with established disease. In the early years of this study, only the total serum calcium was measured and corrected for albumin. At the end of 1986 an analyzer for ionized calcium (Radiometer, Copenhagen) was installed, and in all subsequent screenings at the Royal Hobart Hospital both total and ionized fractions have been measured.

A total of 93 members of one family with MEN 1 had shown biochemical evidence of hyperparathyroidism by the end of 1990. In 60 patients this was associated at first screening with elevations of ACTC. However, in 33 patients (35%), ACTC was found to be normal at first screening. Three of those seen before 1986 were considered to have hyperparathyroidism on the basis of elevation of PTH. In one patient this was confirmed at neck exploration. After measurement of IC became available, the other two patients with elevated PTH but normal ACTC were found to have elevated IC and another 30 patients were identified with normal ACTC but elevated IC. Most of these had normal PTH. In some of these patients ACTC was toward the upper end of the normal range, but in others it was around the midpoint and in a few toward the lower limit of the normal range. It was apparent that the acceptance of IC, rather than ACTC, as a screening test would result in a substantial increase in numbers of patients diagnosed as having MEN 1. We therefore decided to review these patients and assess the supporting evidence from other sources for the diagnosis of hyperparathyroidism and MEN 1 in order to justify a change from the traditional standard of elevated ACTC as the basis of diagnosis.

Patients with elevated ACTC have been compared to those with normal ACTC but raised IC or PTH in terms of age, association with other manifestations of MEN 1, parentage of affected offspring, renal and bone involvement, operative findings, and results of surgery.

Results

Age

Elevation of ACTC was seen in MEN 1 patients of all age groups, with an age range of 11 to 75 years at first diagnosis (Table 1). Elevation of IC with normal ACTC was also seen in MEN 1 patients in all age groups (age range of 13 to 81 years at first diagnosis) but was more predominant in young patients. Up to the age of 30 years, almost half of all patients with elevated IC have normal ACTC. Above the age of 30, the majority of patients with elevated IC also have elevated ACTC, but even in this group 28% have normal ACTC.

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Association with lesions at other sites

Thirty-three (55%) of the 60 patients with elevated ACTC also had evidence of a lesion of the pancreas, pituitary, or adrenal or an intrathoracic carcinoid tumor. Seventeen (52%) of the 33 patients with elevated PTH or IC but normal ACTC had evidence of an endocrine tumor at another site.

Experience of the Zollinger-Ellison (ZE) syndrome in Tasman Family 1 has been the same as that reported in an English family (5) where the syndrome only presented in patients who had elevation of serum calcium and serum gastrin. In four of our symptomatic patients, however, this would not have been detected if the IC had not been measured, because these patients had elevated IC but normal ACTC. All of these patients have undergone neck exploration, and all were found to have four-gland hyperplasia. Restoration of IC to normal levels has resulted in symptomatic improvement and a fall in the level of serum gastrin.

Parenthood

Thirty-three of the patients with elevated ACTC are 35 years old or older. Twenty-three (70%) of these 33 have affected children. Sixteen of the patients with elevated IC but normal ACTC are 35 years or older. Nine (56%) of these 16 have affected children diagnosed with MEN 1.

Patient 646 in Tasman Family 1 genealogy 9 had seven sons and two daughters (4). He had normal prolactin, normal gastrin, and normal ACTC at first testing in 1984. IC was first estimated in 1987 when this patient was 81 years old and was found to be elevated although ACTC remained normal. One son (patient 1548) developed "fits" at the age of 19 which was diagnosed as epilepsy. Over the next 12 years, he spent long periods under psychiatric care and off work. Ultimately surgical exploration revealed an insulinoma and two other adenomas in the pancreas. This resolved his medical and psychiatric problems. Although a daughter (patient 1551) was asymptomatic at first screening for MEN 1, she was found to have gross elevation of serum gastrin and serum prolactin. Computed tomography showed liver metastasis and erosion of the pituitary fossa. Another son (patient 1553) had raised ACTC, raised gastrin, and an adrenal adenoma at first screening. Four of the grandchildren also are clearly affected with three showing lesions of the pancreas and pituitary in addition to hyperparathyroidism.

Renal and bone involvement

Eight of the patients with raised ACTC had renal calculi. Four of these had nephrocalcinosis and one developed widespread cystic bone disease (the single instance of this complication in 93 patients).

Only two of the patients with elevated IC but normal ACTC developed renal calculi; neither of these patients has nephrocalcinosis. However, the case records of one of the patients with raised ACTC—patient 1757 born in 1939 and fully investigated in a urology service in 1965 and 1971—clearly show that he developed multiple calculi and bilateral nephrocalcinosis at a time when measurement of ACTC was within the normal range. Following right renal calculus in 1971, he developed left renal calculus in 1972 and had partial nephrectomy for nephrocalcinosis

Table 1
Age at Diagnosis of 93 Patients with Elevated Serum Calcium

Age (years)	Elevated ACTC	Normal ACTC Elevated IC
10-19	5	6
20-29	14	11
30-39	16	4
40-49	11	6
50-59	7	3
60-69	6	2
70+	1	1
Total	60	33

in 1973. On each occasion the case records show that the diagnosis of hyperparathyroidism was considered but that the level of ACTC was found to be normal. In 1971, it was 9.3 mg/dL (normal 9.0 to 11.4 mg/dL). His family history was not known until 1983 when he was first screened for MEN 1. This revealed gross elevation of serum prolactin at 184 μg/L (normal 11 μg/L) and elevation of ACTC at 2.73 mmol/L (normal 2.10 to 2.60 mmol/L). Ionized calcium was not being measured in 1983, but it is highly likely from our experience with other family members that elevation of IC was present from an early age and at the time that his renal problems developed. One of his children, age 19 years, has a prolactinoma of the pituitary, an adenoma of the pancreas, and elevation of IC but not of ACTC or PTH.

At the age of 44, patient 1757 had ischemic heart disease and hypertension which progressed despite parathyroidectomy. At the age of 49 he had a debilitating stroke and hemiparesis.

Findings at surgery

A total of 54 neck explorations have been conducted in 48 members of Tasman Family 1. Overall, 44 patients had a single neck exploration, three patients had two explorations, and one patient had four explorations.

On 40 occasions surgery was indicated on the basis of symptoms associated with elevated ACTC, but 14 patients had normal ACTC and elevation only of IC. In 39 of the 40 operations associated with elevation of ACTC, hyperplasia of all glands was either identified at operation or indicated by persistence of hypercalcemia after removal of less than 3.5 glands. In one patient removal of a single enlarged gland has been followed by prolonged restoration of normal calcium levels.

Seven of the patients with elevated ACTC had parathyroid glands larger than 3 cm in diameter, and one patient had five of eight enlarged parathyroids in excess of 3 cm and two in excess of 5 cm in diameter.

On 14 occasions, surgery has been carried out on patients who had normal ACTC but either elevated IC or elevated PTH. Hyperplasia of all four glands was identified at first exploration in all 14 patients. Only one patient in this group had a parathyroid exceeding 2 cm in diameter.

Results of surgery

Ten of the 54 neck explorations were carried out elsewhere. Nine of these were performed at major teaching hospitals but on

Table 2
Results of Surgery in MEN 1 (44 Operations, 42 Patients)

	Total	Postoperative Elevation ACTC	Postoperative Elevation IC Normal ACTC
Preoperative elevation ACTC	30	3	6
Preoperative elevation IC normal ACTC	14	0	2

six occasions the diagnosis was simply primary hyperparathyroidism and the surgeon was unaware that the patient had MEN 1. After nine of these 10 operations, postoperative ACTC measurements showed persistent or recurrent elevation of ACTC. We have been unable to obtain a record of the postoperative calcium levels in one case.

There has not been a single negative neck exploration in a member of this family. At least one abnormal parathyroid has been identified on every occasion, regardless of whether the diagnosis was based on elevation of ACTC, PTH, or IC.

Forty-four neck explorations for hyperparathyroidism in 42 patients with MEN 1 from Tasman Family 1 have been carried out in the Royal Hobart Hospital. On 30 occasions both ACTC and IC were elevated. On 14 occasions patients had normal ACTC but elevated IC or PTH preoperatively. In follow-up varying from 1 to 16 years, persistent or recurrent elevation of ACTC has occurred only three times. On measurement of IC, a further eight patients have persistent elevations although ACTC is normal. Six of these are patients who had elevation of ACTC preoperatively. Subtotal parathyroidectomy has restored ACTC to normal levels but IC remains elevated. Two of these are patients whose ACTC was normal preoperatively. Therefore, in these two cases, measurement of ACTC showed normal levels both before and after surgery whereas measurement of IC showed elevated levels both before and after the identification and excision of 3.5 parathyroids (Table 2).

Progress of untreated patients

The majority of patients have been followed for more than three years. Three patients under the age of 30 with normal ACTC but elevated IC at the time of their initial test subsequently showed a rise both in IC and ACTC. In 27 patients, the situation of elevated IC but normal ACTC has been maintained at subsequent testing. A transient exception to this pattern has been observed in our patients during operation or intercurrent illness. The calcium has been monitored in one patient undergoing surgery for testicular torsion, in one patient during hysterectomy for fibroids, in one patient hospitalized for renal colic, and in one patient admitted for the treatment of pneumonia. In each of these patients ACTC became transiently elevated during their illness or operation but returned to normal levels following resolution of the illness or recovery from operation. IC levels remained elevated throughout.

Table 3
Supporting Evidence for MEN 1 in 93 Patients with Elevated Serum Calcium

	Elevated ACTC	Normal ACTC Elevated IC
Lesions at other sites	44 (73%)	23 (70%)
Affected offspring	23	9
Confirmed by surgery or autopsy	34 (57%)	15 (45%)
Lesions at other sites and/or affected offspring and/or confirmed by surgery	44 (73%)	23 (70%)
Total	60	33

Discussion

Benson and colleagues (2) reported in 1987 following a study of three discriminants that IC is a more sensitive predictor of primary hyperparathyroidism than either ACTC or PTH. PTH assays have not been consistently valuable in our study. In the early years, the measurement of C-terminal was used and considered to be unsatisfactory. Later, the introduction of measuring the intact molecule proved to be not always helpful in young patients with MEN 1 who have elevated ACTC or IC. Even a normal level of PTH is inappropriate in these patients and the diagnosis of hyperparathyroidism would only be considered doubtful if PTH were low or absent.

Altogether, 23 (70%) of the 33 patients with elevated IC either have additional evidence of MEN 1 in terms of having another neuroendocrine lesion or having children with other neuroendocrine lesions or else have had the diagnosis of hyperparathyroidism confirmed by surgery. This is virtually identical with the findings in those with elevated ACTC (Table 3). We conclude that the diagnosis of MEN 1 is just as probable in patients with elevated IC but normal ACTC as in those with elevated ACTC.

It has only been possible to measure IC since the end of 1986 and a larger study and prolonged follow-up is necessary to provide firm conclusions regarding the emerging pattern of calcium changes and PTH levels in teenagers as hyperparathyroidism develops. Initial results suggest that it is the normal pattern for IC to become elevated whilst both ACTC and PTH are within the normal range. We have not seen any patients with consistent elevation of ACTC but normal IC. With the passage of time, some patients progress to a situation where both ACTC and IC are elevated. In other patients IC is persistently elevated but ACTC remains normal throughout life except during periods of illness or stress.

Moreover, the age distribution of elevated IC with normal ACTC (Table 1, Figure) indicates that if screening is based on ACTC then diagnosis may not simply be delayed but may never be established. Offspring may then be unaware of their family history. It is inconceivable that the diagnosis of insulinoma would have been missed for 12 years if patient 1548 had given a family history of hyperparathyroidism. Careful assessment of the pancreas, pituitary, adrenal, thymus, and bronchus where more serious lesions may develop will be omitted.

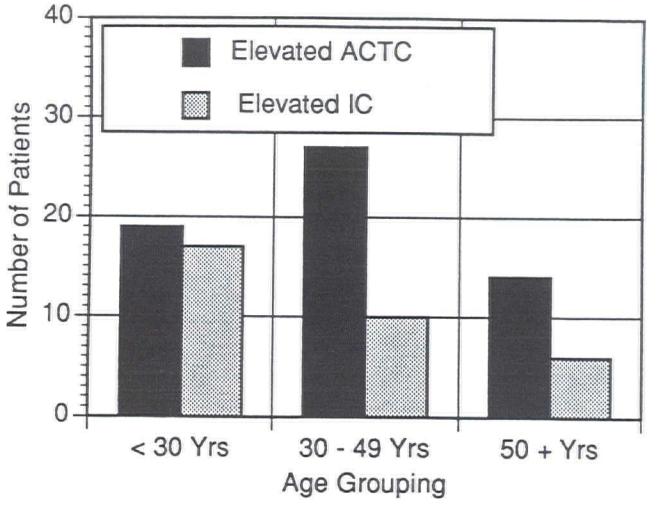
Failure to measure IC may adversely affect the management of intractable ulceration in patients with MEN 1. In this family, every patient with the ZE syndrome and raised serum gastrin also has an elevation of the serum calcium, but in four of the patients only IC was elevated and ACTC was normal. In these four patients, previously intractable ulceration responded to parathyroidectomy without the necessity for gastric surgery. On the other hand, a member of Tasman Family 1 who had migrated to another country underwent three major gastric operations, culminating in total gastrectomy for bleeding ulcer without recognition of her parathyroid hyperplasia. She is not included in our series of 93 patients because IC was never measured and ACTC was normal. She clearly had hyperparathyroidism because at her death from metastasizing malignant carcinoid of the bronchus, postmortem revealed four hyperplastic parathyroid glands up to 2 cm in diameter. A previous history of adrenal and pituitary adenomas had alerted her physicians to the likelihood of MEN 1, but when both ACTC and PTH were found to be normal they considered the diagnosis of hyperparathyroidism as unproven. Our experience suggests that her IC would have been elevated had this measurement been undertaken and her intractable ulcer would probably have responded to parathyroidectomy. Incidentally, this case history indicates that the finding of normal ACTC and PTH in the presence of indisputable hyperparathyroidism in a member of this family is not confined to our institution.

An unwelcome aspect of this study from the surgical viewpoint has been the finding that recurrence or persistence of hypercalcemia after parathyroidectomy is much more common than is apparent when only ACTC is measured. Rather than three recurrences in patients from our own unit identified on the basis of ACTC measurement, it has been found that IC remains, or has again become, elevated in 11 of 44 operations. Our initial experience of finding moderately enlarged glands, compared with those found in patients with elevation of ACTC, led to an earlier philosophy in the patients with normal ACTC of preserving the equivalent of one small gland to avoid hypoparathyroidism. It has now become apparent that these patients need to be dealt with just as radically as those with elevation of ACTC or elevation of IC will persist or recur.

Several studies have reported a higher recurrence rate following parathyroid surgery in patients with MEN 1 than in those with adenomas or hyperplasia from other causes. Following ten operations on members of this family outside our own unit, the recurrence rate has been at least 90%. Prinz et al (6) found a recurrence rate of 33% whilst Rizzoli et al (7) reported 54% recurrence after one operation and 46% after a second neck exploration in MEN 1 patients.

All previous authors appear to have based their figures entirely on the measurement of ACTC. Our experience suggests that the true recurrence rate may be much higher than even the unsatisfactory levels indicated by previous studies and that a radical surgical approach is essential in all patients with MEN 1.

However, the main significance of the operative findings and postoperative studies may be the indication that elevation of IC with normal ACTC reflects to some extent the quantity of hyperplastic parathyroid tissue. Measurement of ACTC establishes the diagnosis of hyperparathyroidism in one-half of patients under the age of 30 and 65% at all ages when four hyperplastic glands are present. However, measurement of ACTC will only establish the diagnosis in one-fourth of patients with persistent hyperparathyroidism associated with one or less than one hyperplastic gland. If a similar situation applies to the early stages of sporadic adenomas, it is possible that ACTC is equally unsuitable to screen members of the general population with renal calculi, osteopenia, or recurrent pancreatitis.



Figure—Age grouping: The designated "elevated IC" group indicates those with elevated IC but normal ACTC.

The finding that many MEN 1 patients have normal ACTC should not be interpreted as indicating that only a modest level of hypercalcemia is a constant finding in the syndrome. Three patients had ACTC levels between 3.5 and 3.9 mmol/L at first diagnosis with two requiring urgent treatment of acute hypercalcemic crisis. Moreover, a sudden rise of IC and a transient rise of ACTC have been observed in four patients after operation or during intercurrent illness, reinforcing the view that in MEN 1 families it is highly desirable to identify all patients with hyperparathyroidism by including the measurement of IC in routine screening.

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