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Familial medullary thyroid carcinoma without associated endocrinopathies: a distinct clinical entity

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In an evaluation of 213 patients from 15 kindreds with familial medullary thyroid carcinoma (MTC), we detected 41 subjects from two kindreds (L and O) who had MTC but no extra-thyroidal manifestations (hyperparathyroidism, phaeochromocytomas or mucosal neuromas) of multiple endocrine neoplasia (MEN) type IIa or IIb. In screening 178 members of the L and O kindreds, we found no evidence that any of them had died from MTC. To assess whether the malignancy was relatively indolent in these families, 20 selected subjects from the two kindreds were compared with 33 MEN IIa subjects. Both groups had clinically occult disease which was diagnosed biochemically by documenting elevated plasma calcitonin (CT) levels following stimulation with intravenous calcium and pentagastrin. There were no differences in the peak stimulated plasma CT levels at the time of diagnosis (1055 ± 236 pg/ml versus *1096 ± 191 pg/ml) or the incidence of regional lymph node metastases (0/20* versus *1/33) in the two groups. The mean age at diagnosis, however, was significantly higher in patients of the L and O kindreds than in patients with MEN IIa (43·1 ± 3·4 years* versus *21·1 ± 2·2 years; P < 0·001) indicating that in the two kindreds the MTC either developed at a later age or grew more slowly. This study demonstrates that MTC may occur in a familial pattern distinct from its presentation as MEN IIa or MEN IIb. In this setting it appears to be the least aggressive form of MTC yet described.*

Keywords: Thyroid cancers, familial medullary thyroid carcinoma, multiple endocrine neoplasia

Medullary thyroid carcinoma (MTC), first described by Hazard and associates in 1959[1], may occur sporadically, as a unilateral lobe thyroid lesion without associated endocrinopathies, or it may present affecting both thyroid lobes and associated with the multiple endocrine neoplasia (MEN) type II syndromes. Multiple endocrine neoplasia type IIa is characterized by the concurrence of bilateral MTC, phaeochromocytomas and parathyroid hyperplasia. Multiple endocrine neoplasia type IIb is typified by bilateral MTC and phaeochromocytomas in the setting of a characteristic phenotype consisting of multiple mucosal neuromas and ganglioneuromatosis of the gastrointestinal tract. Multiple endocrine neoplasias type IIa and IIb are inherited as an autosomal dominant trait. Some cases of MEN IIb appear to be genetic mutants and even though there is no prior history of familial disease half their offspring will be affected should they survive to procreation. Previous reports[2–4] have suggested a fourth pattern of MTC. A few patients have been reported who appeared to inherit MTC as an autosomal dominant trait without associated endocrinopathies. Because of limited screening and the small number of patients studied, however, uncertainty has existed regarding the exclusion of adrenal or parathyroid disease.

The present report documents the familial occurrence over four generations of MTC in two kindreds in which the presence of phaeochromocytoma and hyperparathyroidism was excluded by extensive testing. The MTC in these kindreds developed relatively late in life and seemed never to have caused death of the host. Medullary thyroid carcinoma thus appears much less aggressive in these kindreds than when it occurs sporadically or in patients with MEN IIa or MEN II b.

Materials and methods

Patients

We studied 176 members of two families with known MTC. Thirty-five individuals from four generations of kindred L (*Figure 1*) have been evaluated since 1972. Twelve (3 males and 9 females) subjects developed MTC and the mean age at diagnosis was 33·6 years (range 15–72 years). One hundred and forty-one members of four generations of kindred O (*Figure 2*) have been similarly evaluated over the past 36 months. Of these, 29 (18 males and 11 females) were found to have MTC, and the mean age at diagnosis was 49·6 years (range 17–68 years).

Clinical evaluation, treatment and follow-up were performed either at the Duke University Medical Center, Durham, North Carolina, the Johns Hopkins Hospital, Baltimore, Maryland or the Walter Reed Army Hospital, Washington, D.C.

Methods of screening

Medullary thyroid carcinoma. The diagnosis of MTC was suggested in some patients by the presence of a thyroid mass. The diagnosis, however, was confirmed in these and other kindred members at risk by detecting elevated (> 300 pg/ml) levels of plasma calcitonin (CT) either in the basal state or following the concomitant intravenous administration of calcium (2 mg/kg in 1 min) and pentagastrin (0·5 μg/kg in 5 s). The technique of provocative testing[5,6] and the method of radioimmunoassay for CT[7,8] have been described previously.

Hyperparathyroidism. To assess parathyroid function, total serum calcium was determined utilizing an atomic absorption spectrophotometer (model 151, Instrumentation Laboratory, Lexington, Massachusetts). Serum parathyroid hormone (PTH) was determined by radioimmunoassay with carboxyl-terminal specific antisera as previously described[9]. Serum concentrations of phosphorus, chloride, and alkaline phosphatase were determined by the Technicon

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Autoanalyser. At thyroidectomy parathyroid glands were examined grossly and histologically by selective biopsy.

Phaeochromocytoma. Preliminary evaluation for phaeochromocytoma included determination of 24 h urinary excretion rates of adrenaline, noradrenaline, vanillylmandelic acid (VMA), and metanephrines. The concentrations of adrenaline and noradrenaline were determined fluorometrically[10]. Spectrophotometric analysis was utilized in the measurement of urinary VMA and metanephrines[11,12]. Some of the metanephrine analyses were performed by a fluorometric method[13].

Abdominal computerized tomographic scans were performed in ten members of kindred O with biochemically proven MTC. Transverse images of 5–10 mm thickness were obtained through the expected location of each adrenal gland.

Surgery

Medullary thyroid carcinoma was treated by total thyroidectomy with resection of the lymph nodes in the central zone of the neck. When parathyroid gland viability was uncertain they were autotransplanted to the sternocleidomastoid muscle. Small parathyroid biopsies were submitted for histological study. Postoperatively L-thyroxin was given as replacement therapy.

Postoperative evaluation

All affected members of the L and O kindreds have been evaluated annually by physical examination and by determinations of serum calcium, urinary catecholamine and basal and stimulated plasma CT levels.

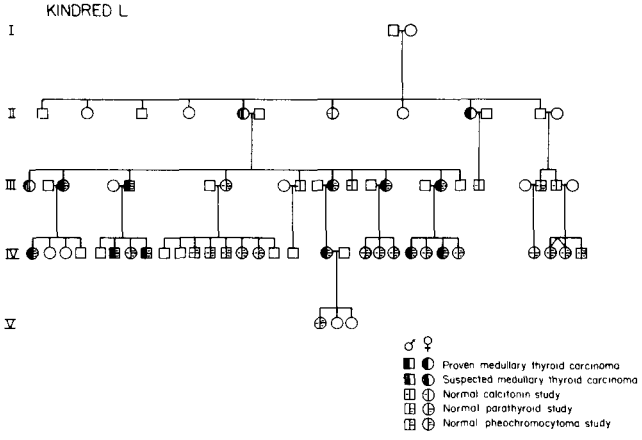

Figure 1 *The genealogy of 5 generations of kindred L is shown. Test and disease status of individual members is shown in the key. No symbols for parathyroid disease or phaeochromocytoma are shown, since no individuals were positive for these disorders*

Results

Medullary thyroid carcinoma

One hundred and seventy-six members of the L and O kindreds were evaluated and MTC was detected in 41. Six patients had palpable thyroid lesions and 35 patients had clinically occult disease which was detected biochemically by plasma CT assay. Of this latter group, 4 had elevated basal plasma CT levels and 31 had elevated levels following provocative stimulation with calcium (Ca^{2+}) and pentagastrin (Pg).

Thirty-seven patients were treated by total thyroidectomy; 4 patients declined surgery. Evaluation of the thyroid in each case confirmed the diagnosis of MTC (29 patients) or C-cell hyperplasia (8 patients). Metastases to regional lymph nodes were evident histologically in 3 (10 per cent) of 31 patients with a palpably normal thyroid who were diagnosed by biochemical testing. Following total thyroidectomy, stimulated plasma CT levels were elevated (>300 pg/ml) in 3 (50 per cent) of the 6 patients with palpable disease and in 4 (13 per cent) of the 31 patients whose disease was detected biochemically.

In scanning the 176 members of the L and O kindreds, careful family histories were taken. We could find no evidence that anyone in the two kindreds had died from MTC. Furthermore, it appeared that the MTC had its onset relatively late in life. To test this hypothesis, we compared 20 patients from the L and O kindreds with 33 patients with MEN IIa. Patients in the two groups were selected for similarity of MTC tumour burden. They had no palpable thyroid disease and their basal plasma CT levels were <200 pg/ml but increased following provocative stimulation with calcium and pentagastrin. It had previously been shown[5] that there was a direct correlation between pre-operative stimulated plasma CT levels and the extent of MTC.

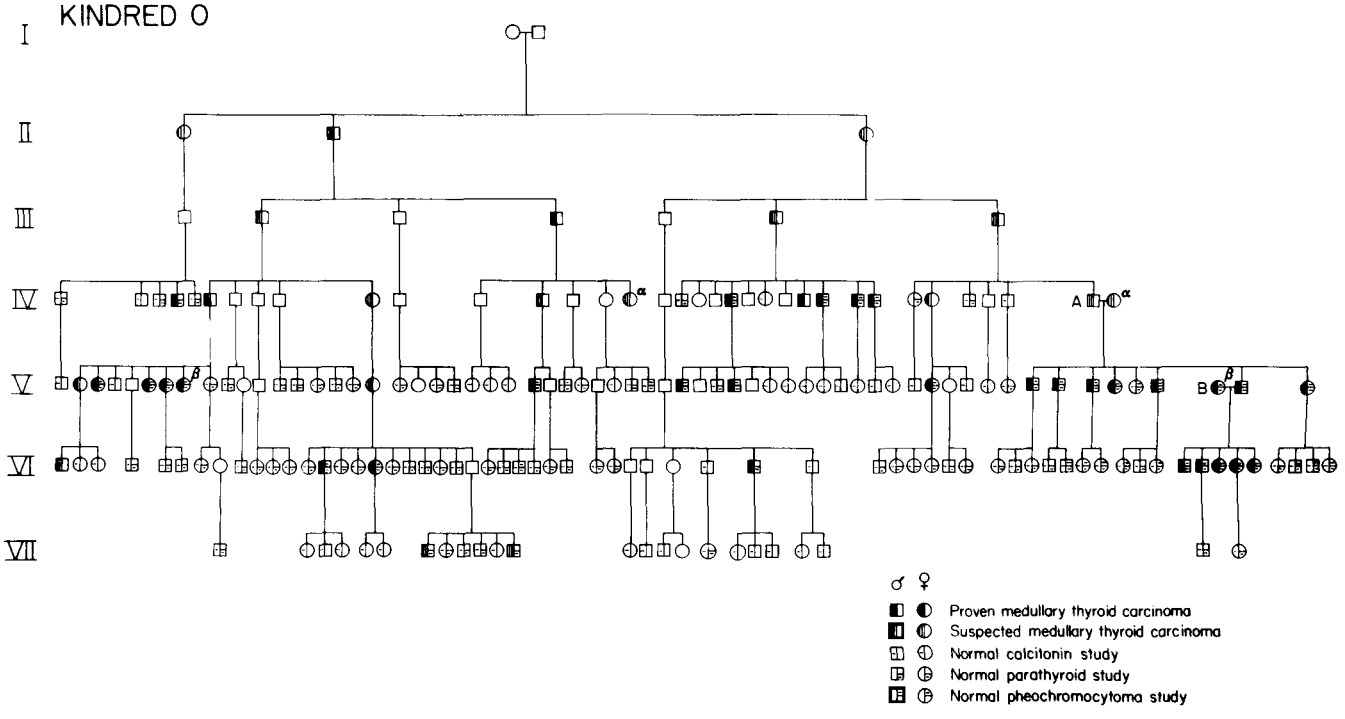

Figure 2 *The genealogy of 7 generations of kindred O is shown. The key is the same as for* Figure 1. *For convenience, spouses are not shown, except for the two consanguineous marriages, A and B. Two individuals, α and β, each appear twice on the figure; they are the wives involved in the consanguineous marriages*

Table 1 *Comparison of patient groups*

Patients	Mean age (years)	Stimulated plasma calcitonin value (pg/ml)	Metastases	Postoperative residual medullary thyroid carcinoma
L and O ($n=20$)	43·1 ± 3·4	1055 ± 236	0/20	2/20
	$P<0·001$	P=n.s.	P=n.s.	P=n.s.
MEN IIa ($n=33$)	21·1 ± 2·2	1096 ± 191	1/33	3/33

Even though there was no significant difference in the mean stimulated plasma CT levels in the 20 members of the L and O kindreds (1055 ± 236 pg/ml), compared to the 33 patients with MEN IIa (1096 ± 191 pg/ml), the mean age at diagnosis of MTC was 43·1 ± 3·4 years in the former and 21·1 ± 2·2 years in the latter ($P<0·001$) (*Table 1*).

Twelve of the 29 patients in kindred O with proven MTC were the offspring of two, (A and B), apparently consanguineous marriages (*Figure 2*). Both parents in Family A were suspected of having MTC (by history and medical records) although both had died (at 72 and 68 years of age) before our study. Seven of their eight offspring had MTC. Family B was formed from the union of one of the affected sons of Family A with an affected female kindred member, and all five of their offspring subsequently developed the disease. Assuming that each parent in both consanguineous marriages was heterozygous, the expression of MTC in the offspring might be more severe in the 25 per cent of children who would be expected to be homozygous for the gene causing MTC.

To investigate this possiblity we evaluated four parameters indicative of early development and rapid growth of MTC: mean age (MA) at the time of diagnosis, stimulated plasma CT at the time of diagnosis, regional lymph node metastases at the time of surgery, and residual medullary thyroid carcinoma postoperatively as evidenced by elevated stimulated plasma CT levels. Twenty-seven affected members of the O kindred who had total thyroidectomy, 12 from consanguineous and 15 from nonconsanguineous marriages, were studied (*Table 2*). The MTC may have indeed been more aggressive in the 12 offspring of the consanguineous marriages because in them the tumour developed at a significantly earlier age, their pre-operative CT levels were higher, and the presence of metastases and residual medullary thyroid carcinoma were largely confined to their group. The differences between the two groups, for all four parameters, were statistically significant, except for residual medullary thyroid carcinoma (*Table 2*).

Hyperparathyroidism

One hundred and thirty-two members of the L and O kindreds including 37 patients with surgically proven MTC (or C-cell hyperplasia) had normal concentrations of serum calcium (2·1–2·55 mmol/l). In 96 of these subjects, plasma levels of PTH were measured and found to be normal. One normal subject had an increased plasma PTH level but a normal concentration of serum calcium. Gross and microscopic examinations of parathyroid tissue in 26 members of the L and O kindreds showed normal sized glands and normal cellular histology. Postoperative annual screening has not detected subsequent hypercalcaemia.

Phaeochromocytoma

Urinary excretion rates of adrenaline, noradrenaline, VMA and metanephrines were normal in 66 members of the L and O kindreds. Thirty-seven of these patients had surgically proven MTC or C-cell hyperplasia.

Abdominal scans performed on 10 members of kindred O with proven MTC were normal. Both adrenal glands were identified in 8 patients. Having obtained no abnormal biochemical markers of phaeochromocytoma in these patients scanning was then discontinued as being unlikely to uncover 'biochemically silent' adrenal tumours. Subsequent postoperative annual clinical evaluation and urinary catecholamine determinations have not provided evidence for asynchronous development of phaeochromocytoma.

Discussion

This study documents the occurrence of 'familial non-MEN MTC', a hereditary form of medullary thyroid carcinoma existing as a distinct clinical entity with none of the other stigmata of the MEN II syndromes.

Several authors have reported families in which MTC appeared to occur in the absence of associated endocrinopathies[2–4]. In most, however, the number of family members screened was small, and the methods of excluding the presence of hyperparathyroidism and phaeochromocytoma were not specified. In 1967, Block *et al.*[2] reported two families with 7 and 3 affected members but the propositus of the first family had a parathyroid adenoma and neither family was tested for other endocrinopathies. Six years later, Jackson[3] reported the screening of 19 members of a kindred with proven MTC, but urinary catecholamines were obtained in only three individuals. In the most definitive report to date, Block *et al.*[4] described three families in which MTC appeared to be the sole endocrine lesion. One of these families was discussed in depth and 17 and 10 members were screened for MTC and phaeochromocytoma, respectively. Seven individuals had proven or suspected MTC, and none had parathyroid or adrenal disease. The other two families had only two affected individuals each.

In the present work, 176 members of two separate kindreds were carefully evaluated for the presence of MTC, phaeochromocytomas and hyperparathyroidism. There was no biochemical or radiographic evidence of phaeochromocytomas, nor was there biochemical, macroscopic or microscopic evidence of HPT in any individual studied. Familial non-MEN MTC may be more prevalent than is generally recognized. From our investigations of 15 kindreds with MTC, two have been classified as familial non-MEN MTC.

Although the currently described entity is similar in many ways to MEN IIa and MEN IIb (autosomal dominant mode of inheritance and bilaterality of MTC), there are many features which mark it as a distinct clinical entity. Most noteworthy are the lack of endocrine and neuroectodermal disorders associated with MEN IIa or MEN IIb and the non-aggressive clinical behaviour of the MTC. The much later mean age of diagnosis of MTC in our two reported kindreds despite similar presentations and pre-operative stimulated plasma CT levels can best be explained by either a later age of onset of MTC or more indolent tumour growth. Indeed MTC was diagnosed at an early stage (stimulated plasma CT levels of 500 pg/ml and 1200 pg/ml) in two subjects aged 61 and 65 with very small foci of MTC, detected bilaterally at surgery, but with no regional lymph node involvement.

Of the 213 patients with MTC whom we have evaluated over

Table 2 *Comparison of marriage groups*

Kindred O	Mean age (years)	Stimulated plasma calcitonin value (pg/ml)	Metastases	Postoperative residual medullary thyroid carcinoma
Nonconsanguineous ($n=15$)	54·8 ± 2·4	2·4 ± 0·8	0/15	1/15
	$P=0·001$	$P=0·02$	$P=0·028$	P=n.s.
Consanguineous ($n=12$)	41·0 ± 3·5	40·5 ± 19·7	4/12	3/12

the last 10 years, 21 (15 per cent) of 136 patients with MEN IIa, 5 (50 per cent) of 10 patients with MEN IIb and 8 (31 per cent) of 26 patients with sporadic MTC have succumbed to thyroid carcinoma. None of the 41 patients with familial non-MEN MTC, nor members of the L and O kindreds, have died of MTC. We recommend total thyroidectomy in patients with sporadic MTC, MEN IIa or MEN IIb since disease progression of the thyroid malignancy in these clinical settings, even though variable, is relentless[13,14]. Although some investigators might argue that patients with familial non-MEN MTC should be followed expectantly and not have thyroid extirpation, especially if they are elderly, we have advised thyroidectomy in these patients.

It was of interest in one of our kindred that there were two instances where two affected and probably related subjects married one another. In the offspring of these affected parents, compared to children of only one affected parent, the MTC developed at an earlier age (41·0 *versus* 54·8 years) and there was evidence of more aggressive tumour growth: increased frequency of metastases to regional lymph nodes, and increased incidence of residual medullary thyroid carcinoma postoperatively. These differences presumably resulted from homozygosity for the MTC gene which would be expected in at least 25 per cent of the offspring of these consanguineous marriages. We have not followed the children of these marriages long enough to evaluate the clinical course of the MTC.

Studies in our 13 kindreds with 'classical' familial MEN IIa[5], and in the families of other institutions[4], demonstrate asynchrony of glandular disease presentation with the majority presenting with MTC, a lesser proportion with phaeochromocytoma and a minority with primary hyperparathyroidism. This pattern has not been seen in these two kindreds (L and O) but, clearly, does not preclude indolent phaeochromocytomas or parathyroid abnormalities which may declare themselves much later. Members of kindred L have been followed by annual screening since 1972 and members of kindred O since 1978, making this possibility unlikely. The detection of an apparently indolent medullary thyroid carcinoma in an elderly patient with no evidence of phaeochromocytoma or hyperparathyroidism, therefore, cannot be assumed to mean that the patient has 'familial non-MEN MTC' until careful family history and screening are undertaken.

In conclusion, this study demonstrates that MTC can occur as an autosomal dominant trait without associated endocrinopathies. Although similar in many of its clinical and histological aspects to other forms of MTC, this disease has many features which establish it as a distinct clinical entity.

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