Incidental detection of familial medullary thyroid carcinoma by calcitonin screening for nodular thyroid disease

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Abstract
Serum calcitonin screening has recently been found to be a useful supplement to fine-needle aspiration biopsy, ultrasound and radionuclide imaging in the evaluation of thyroid nodules. We describe a case where introduction of routine calcitonin screening in nodular thyroid disease led to the detection of a family with medullary thyroid carcinoma. The benefits and problems of basal and stimulated serum calcitonin testing and ret-proto-oncogene mutation studies are exemplified and we discuss the appropriate use and interpretation of these tests. We conclude that routine basal serum calcitonin measurement in nodular thyroid disease and thoughtful use of ret-mutation analysis is cost-effective in detecting medullary thyroid carcinoma and multiple endocrine neoplasia type II.

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Introduction
Nodular thyroid disease is a very common clinical problem. Approximately 15% of adults in iodine-deficient areas like Germany have thyroid nodules on ultrasound (1). The primary goal in the work-up of thyroid nodules is to distinguish patients with cancer from those with benign disease. Diagnostic criteria are sonomorphological appearance and size, cytological features in fine-needle aspiration biopsies and radionuclide uptake on scinti-scans (2). Laboratory studies were generally regarded to be of low diagnostic yield, until recent studies involving more than 3000 patients found that measurement of basal serum calcitonin levels is a sensitive and specific method for the detection of patients with medullary thyroid carcinoma (MTC) (3–7). This approach appears to be cost-effective (8) for a tumor that accounts for approximately 1% of nodular thyroid disease and is not readily detectable by other means (6).

We therefore introduced routine measurement of basal calcitonin levels for all patients with nodular thyroid disease at our institution. Here we describe a prismatic case, where a single basal serum calcitonin level led to the disclosure of a new pedigree of familial MTC.

Methods
Measurement of basal serum calcitonin levels and levels 2, 5 and 10 min after injection of pentagastrin (Peptavlon; Zeneca Pharma, Cergy, France; 0.5μg/kg body weight) was performed with an immunoradiometric assay (Cis-Bioindustries, Gif sur Yvette, France). Thyroid tissue was examined by standard techniques and immunochemistry using an anti-calcitonin antibody. Mutation screening was performed by PCR amplification of exons 10, 11, 13, 14, 15 and 16 from peripheral blood leukocyte DNA and direct sequencing of the PCR products (Thermo-Sequenase; Amersham, Braunschweig, Germany).

Case report
In 1978 a 39-year-old Caucasian woman presented at our institution for thyroid evaluation because of increased nervousness and sweating. Physical examination showed a moderately enlarged right thyroid lobe without palpable nodules and thyroid function was normal. In 1990, ultrasound revealed a single right-sided thyroid cyst of 13×9 mm with surrounding hypodense areas. A radionuclide scan showed homogenous uptake, thyrotropin and thyroid hormone levels were normal and the patient was scheduled for re-examination once a year. When the patient reappeared in 1997 the cyst was 14×8 mm and adjacent to it a 5×5 mm hypodense nodule could be seen. A repeated scinti-scan was normal and we obtained a basal calcitonin level for the first time which was 181 pg/ml and rose to a maximum of 5850 pg/ml 2 min after pentagastrin stimulation. Total thyroidectomy was performed; pathological examination revealed multiple foci of MTC in both lobes (Fig. 1).
Analysis of the \textit{ret}-proto-oncogene showed a heterozygous TTG to TTC germline mutation of codon 790 in exon 13 changing leucine to phenylalanine (Fig. 2). This mutation has recently been shown to cause familial MTC and multiple endocrine neoplasia type 2 (MEN2) (9). The patient has two daughters; both had no history of thyroid disease. Physical examination, thyrotropin and thyroid hormone levels were unremarkable in both daughters, but ultrasound revealed a thyroid nodule in daughter 1 (27 years). Pentagastrin-stimulated calcitonin levels were measured. Daughter 1 had a basal level of 12 pg/ml which rose to a maximum of 97 pg/ml 2 min after pentagastrin, daughter 2 (24 years) had a basal level of 4 pg/ml and showed no stimulation. Mutation studies revealed that daughter 2 had a normal genotype, whereas daughter 1 had inherited the codon 790 mutation from her mother (Fig. 1). She has meanwhile undergone prophylactic thyroidectomy and histology confirmed c-cell hyperplasia with small foci of MTC. None of the patients had evidence for pheochromocytoma or hyperparathyroidism.

\textbf{Discussion}

Work-up strategies for thyroid nodules have been extensively studied. Varying amounts of dietary iodine cause differences in the prevalence of thyroid nodules and lead to regional preferences in the use of thyroid ultrasound, fine-needle aspiration biopsies and radio-nuclide scans. In both iodine-deficient and iodine-rich regions of the world, however, laboratory studies are usually only employed to exclude hyperthyroidism or thyroiditis (2).

Several studies convincingly demonstrated that calcitonin screening for MTC in nodular thyroid disease is efficacious (3–7), and must thus be regarded an important part of the initial evaluation of thyroid nodules. It has, however, also been shown that there is a considerable overlap in basal serum calcitonin levels between patients with MTC and normal controls (10, 11). Because of this lack of a clear-cut normal range, it is critical to define appropriate cut-off values for basal and pentagastrin-stimulated calcitonin levels. Many studies used an upper limit of 10 pg/ml for unstimulated and 100 pg/ml for stimulated levels. Daughter 1 of the pedigree described here highlights this problem as her basal and stimulated calcitonin levels were not diagnostic. Thus, a threshold of 100 pg/ml for stimulated serum calcitonin may be too high for patients with hereditary MTC. Barbot et al. (3) have presented data that support this view, because eight of ten patients from MTC families with stimulated serum calcitonin levels between 30 and 100 pg/ml had MTC. This finding has important consequences for screening policies, as up to 10% of seemingly sporadic MTCs finally turn out to be hereditary (8). Another study (12) found that peak stimulated calcitonin levels rarely exceed 30 to 50 pg/ml.
in healthy volunteers and genetically unaffected members of MEN2 families. This suggests that stimulated calcitonin levels above 50 pg/ml might be considered pathologic.

There is, however, a considerable overlap in stimulated calcitonin levels between normal subjects and ret-mutation carriers (10, 11). Simply lowering the calcitonin threshold level would indeed provide a better sensitivity, but would lead to an unacceptable high number of false positives. This is caused by a huge difference in the prevalence of MTC between patients with undetected ret-mutations and the general population. Because the negative predictive value of a test strongly depends on the prevalence of the disease in the tested population, the best way would be to adjust the cut-off accordingly.

The diagnostic dilemma is that at first the individual risk for MTC of a patient with a thyroid nodule is unknown. It is therefore tempting to perform tests for germline ret-proto-oncogene mutations for patients with borderline basal or stimulated calcitonin. The risk for MTC in such a population will be somewhere between 1% the overall prevalence of MTC, and 40% the prevalence in patients with basal serum calcitonin levels above 10 pg/ml (6). Because only 10% of these will have ret-mutations, ret-testing will be uninformative in more than 96% of the patients. This approach therefore does not seem to be clinically useful and cost-effective, unless the actual risk of MTC for patients with borderline serum calcitonin levels can be defined more precisely by future studies.

Meanwhile, careful evaluation of the family history for evidence of MEN2 or familial MTC may be the best way to identify patients at excess risk for MTC and justify genetic testing (13). Otherwise, clinical follow-up, looking for other reasons for elevated calcitonin levels (14–18), and repeated calcitonin studies appear to be an appropriate approach to patients with stimulated calcitonin levels between 30 and 100 pg/ml.

In every case of proven MTC, however, genetic testing for germline ret-proto-oncogene mutations is indicated. Beside the common mutations in exon 10 (codon 609, 611, 618, 620), exon 11 (codon 630, 631), exon 13 (codon 768, 790, 791), exon 14 (codon 804, 844) and exon 15 (codon 883, 891) seems appropriate, because these latter mutations make up a considerable proportion of mutations in seemingly sporadic MTCs (9). Although experience of genotype–phenotype relations and the clinical course of patients with these rare mutations is limited, there appears to be a more variable penetrance and considerable variance in the onset of the disease. In a series of 23 patients, the youngest patient with a manifestation of the disease was 21 years, whereas the oldest confirmed gene carrier without detectable disease activity was 71 years (9). Because of the grave consequences of advanced MTC, it nevertheless seems prudent to perform total thyroidectomy as soon as the pathogenic mutation is identified.

This prismatic pedigree with two cases of occult MTC caused by familial MTC exemplifies the importance of measuring unstimulated serum calcitonin levels as part of the primary work-up in patients with nodular thyroid disease. As soon as MTC has been found, genetic testing for all known mutations in the ret-proto-oncogene is desirable. Using both tests appropriately can help to achieve an early diagnosis of MTC with a high probability of surgical cure (19, 20).

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References


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