Early or prophylactic thyroidectomy in MEN 2/FMTC gene carriers: results in 71 thyroidectomized patients

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Abstract

Background: Once genetic testing accurately identifies MEN 2 gene carriers, affected children are given the opportunity to undergo thyroidectomy at the earliest stages of the C-cell disease.

Objective: To define reliable parameters by which to identify the best moment for thyroidectomy in patients who are carriers of the MEN 2 gene.

Patients and methods: Seventy-one MEN 2/FMTC gene carriers, collected through the national register of the French Calcitonin Tumours Study Group, were evaluated. All the patients included were younger than 20 years of age and underwent total thyroidectomy. Basal and pentagastrin-stimulated calcitonin were assayed using an immunoradiometric method (sensitivity less than 2 pg/ml). Calcitonin measurement was evaluated on the basis of histopathological findings in surgical thyroid specimens.

Results: We found C-cell hyperplasia or medullary thyroid carcinoma in all the 71 gene carriers – even for the youngest patients – and nodal metastases were present in four cases. Calcitonin measurement (basal or pentagastrin-stimulated) detected C-cell disease preoperatively in all patients. Six of the 71 patients were not surgically cured: one had nodal metastases, one had an advanced staged disease and four had an incomplete nodal dissection or had not undergone lymph node surgery.

Conclusions: Determination of calcitonin forms an integral part of the management of MEN 2 gene carriers. Thyroidectomy is undisputably indicated when basal calcitonin is abnormal. When basal calcitonin is undetectable, a pentagastrin-stimulated increase in calcitonin to more than 10 pg/ml indicates an early thyroidectomy to cure the patient.

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Introduction

Medullary thyroid carcinoma (MTC) may occur in a sporadic or a hereditary form as a part of multiple endocrine neoplasia type 2 (MEN 2). MEN 2 is an autosomal dominant inherited multiglandular syndrome with age-related penetrance, three variants of which have been identified. MEN 2A (60% of cases of MEN 2) associates MTC, phaeochromocytoma and hyperparathyroidism. MEN 2B (5% of cases of MEN 2) associates MTC, phaeochromocytoma, Marfanoid habitus, mucosal neuromas, and ganglioneuromatosis of the gastrointestinal tract. Familiar MTC (FMTC; 35% of cases of MEN 2) occurs in families in the absence of the other manifestations of MEN 2.

In hereditary forms, C-cell hyperplasia is the earliest histological finding that precedes microcarcinoma, then fully expressed MTC, classically multifocal and bilateral, which is the most common cause of death among these patients. Lymph node metastases are present in 43–63% of patients when MTC is clinically detected, but may also occur concomitantly with a microcarcinoma (1). As surgery is the only curative treatment of MTC, it is clear that early diagnosis is crucial (1–5).

Inheritance of MTC is related to the presence of germ-line mutations in the proto-oncogene RET, in 95% of MEN 2B, and in 98% and 88% of MEN 2A and FMTC kindreds, respectively (6, 7). Genetic testing by direct DNA analysis provides the opportunity to detect subjects at risk, and...
high basal or pentagastrin-stimulated calcitonin indicates the presence of C-cell disease. Several reports (3, 5, 8) have largely demonstrated the benefit of RET genetic testing in the management of MEN 2 families, which leads to the identification of gene carriers and enables prophylactic thyroidectomy to be performed (5, 8–14). The rationale for this approach is based on the assumption that an earlier diagnosis should make the surgery curative.

Once genetic testing accurately determines MEN 2/FMTC gene carriers, several questions arise. What does measurement of calcitonin play in the decision to operate? At what age should total thyroidectomy be performed? What should be the surgical procedure?

To obtain more insight into these questions, we evaluated 71 thyroidectomized MEN 2/FMTC gene carriers, younger than 20 years of age, collected through the French Calcitonin Tumours Study Group (GETC).

Patients and methods
Seventy-one MEN 2/FMTC gene carriers (34 female and 37 male), aged from 10 months to 20 years (mean age 12.5 ± 5 years) were included. Among them, 51 and 17 patients were from 33 and 10 distinct MEN 2A and FMTC kindreds, respectively, and three were members of three MEN 2B kindreds. All the patients were screened by DNA analysis (direct DNA sequence analysis or linkage analysis). All the patients underwent physical examination, measurement of both basal and pentagastrin-stimulated calcitonin concentrations (except three patients in whom had only basal calcitonin measurements were made) and measurement of urinary excretion of 24-h catecholamine metabolites, and plasma calcium and parathyroid hormone (1–84) concentrations. Informed consent was obtained for all diagnostic and therapeutic procedures.

Calcitonin assay
Plasma calcitonin was measured by an immunometric assay (Elsa-hCT, Cis-BioInternational, Gif sur Yvette, France) based on two monoclonal antibodies that recognize the 11–17 and 24–32 regions of the calcitonin molecule, respectively. There is no cross-reaction with pro-calcitonin, and this method is considered specific for the mature calcitonin monomere. The functional sensitivity of the assay was 2 pg/ml. The intra- and interassay coefficients of variation were 6.7% and 7.9%, respectively, for values between 30 and 100 pg/ml. Basal calcitonin values ≤10 pg/ml were considered normal, according to the data of the GETC (15).

Pentagastrin stimulation test
An i.v. injection (0.5 μg/kg) of pentagastrin (Peptavlon, Zeneca Pharma, Cergy, France) was given for 3 min. Blood samples were collected before and 3, 5, and 10 min after the initiation of the pentagastrin injection. The response was expressed as the maximal peak calcitonin value after the initiation of the pentagastrin injection. Pentagastrin-stimulated calcitonin values were considered normal with reference to the data from the GETC, in which the calcitonin peak did not exceed 15 pg/ml in non-gene carriers younger than 20 years of age (16).

Surgical procedures
Total thyroidectomy was performed in all 71 patients and was associated with lymph node surgery in 61 of them (85.9%). Nodal dissection was restricted to the central compartment in 18 patients, or central dissection was associated with either lymph node harvesting in laterocervical compartments (13 patients) or bilateral laterocervical dissection (17 patients). In four patients, lymph node dissection was restricted to bilateral laterocervical compartments. Nine patients underwent only lymph node harvesting, either restricted to the central compartment (n = 3) or to the ipsi- or bilateral laterocervical compartments (n = 4), or involving both (n = 2). Ten patients had no lymph node surgery at all.

Histopathological examination
The thyroid surgical specimens were examined by a standard histopathological technique. An extensive search for C-cell hyperplasia or microscopic MTC loci was conducted by immunochemistry with an anti-calcitonin polyclonal antibody (CT-205, Immunotech, Marseille, France). The immunohistological criteria used to define C-cell hyperplasia were either a C-cell density of more than 50 C-cells/cm² (×40) or microscopic foci containing more than 6–10 C-cells per field (×40) (17).

Follow-up
Basal and pentagastrin-stimulated calcitonin concentrations were measured postoperatively and serially to detect recurrent MTC. The mean duration of follow-up was 4 years (range 3 months to 10 years).

Statistical analysis
Data analysis included one-way ANOVA or Wilcoxon’s signed rank test, as appropriate. Results are expressed as mean ± s.d. A P value < 0.05 was considered significant.

Results
Preoperative calcitonin concentrations
Fifty-three patients (74.6%) had abnormal basal preoperative calcitonin concentrations (Table 1). Eighteen
patients (7–20 years of age) exhibited normal calcitonin values—that is, $\leq 10$ pg/ml. Mean age did not differ between patients with normal or abnormal basal calcitonin concentrations ($12.7 \pm 4$ and $12.5 \pm 5$ years, respectively); however, patients with the highest basal calcitonin concentrations were older (mean age 18 years), although this difference was not significant (Table 1).

Pentagastrin testing was performed systematically in 68 of the 71 patients. Pentagastrin-stimulated calcitonin values ranged from 18 to 52 800 pg/ml. Seventeen patients had a normal basal calcitonin concentration, but exhibited an abnormal pentagastrin-stimulated calcitonin response ranging from 18 to 520 pg/ml (mean calcitonin peak 139 pg/ml; Table 2).

**Histopathological findings**

All the patients had C-cell disease on thyroid specimens: 66 (93%) had MTC, but five patients had only diffuse and bilateral C-cell hyperplasia. Table 3 shows details of the histopathological findings. C-cell disease was already present in the 18 patients with normal basal calcitonin (Table 2). We revealed a significant relationship between the stage of the C-cell disease and both age and basal calcitonin concentrations by comparing three groups of patients: those with C-cell hyperplasia or MTC <1 mm (group 1, $n = 9$); those with MTC ranging from 1 to 10 mm (group 2, $n = 54$); and those with MTC >10 mm (group 3, $n = 7$). Patients from group 3 had significantly higher basal calcitonin concentrations (mean 574 pg/ml) than those in groups 1 and 2 (means 12.4 and 37.9 pg/ml, respectively; $P < 0.0001$) (Fig. 1a). Mean basal calcitonin concentrations were lower in group 1 (mean 12.4 $\pm 6.6$ pg/ml) than in group 2 (mean 37.9 $\pm 57.4$ pg/ml), but the difference was not significant because of the scatter of calcitonin values in group 2. Patients from group 3 were significantly older (mean age 17 $\pm 2.9$ years) than

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**Table 1** Mean age and preoperative basal calcitonin (CT) concentrations in the 71 thyroid-ectomized MEN 2/FMTC gene carriers.

<table>
<thead>
<tr>
<th>Preoperative basal CT (pg/ml)</th>
<th>Patients (n)</th>
<th>Mean age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq 10$</td>
<td>18</td>
<td>12.7</td>
</tr>
<tr>
<td>11–50</td>
<td>38</td>
<td>12.2</td>
</tr>
<tr>
<td>51–100</td>
<td>5</td>
<td>13.2</td>
</tr>
<tr>
<td>101–500</td>
<td>7</td>
<td>11.7</td>
</tr>
<tr>
<td>$&gt; 500$</td>
<td>3</td>
<td>18</td>
</tr>
</tbody>
</table>

* CT was assayed as described in Methods, and normal ranges were determined according to data from GETC (15).
† CT values were 584, 710 and 2250 pg/ml, respectively.

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**Table 2** Mean age, preoperative pentagastrin-stimulated calcitonin (CT) concentrations, and histopathological findings in the 17 thyroidectomized MEN 2/FMTC gene carriers with normal preoperative basal CT values ($\leq 10$ pg/ml) who underwent a pentagastrin (Pg) test.

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Mean age (years)</th>
<th>Pg-stimulated CT peaks (pg/ml)</th>
<th>Histopathological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$\leq 10$</td>
<td>MTC &lt; 1 mm; CCH</td>
</tr>
<tr>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1</td>
<td>17</td>
<td>11–30</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>11.6</td>
<td>31–100</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>$&gt; 100$</td>
<td>–</td>
</tr>
</tbody>
</table>

* CT was assayed as described in Methods, and normal ranges were determined according to data from GETC (15).
† Pg-stimulated CT $\leq 30$ pg/ml or $< 15$ pg/ml are considered as a normal CT response in healthy adults and normal individuals younger than 20 years of age, respectively, according to data from GETC using the assay described in Methods (15, 16).
‡ Pg-stimulated CT value in this patient.
§ Pg-stimulated CT peaks were 111, 132, 133, 353, 420 and 520 pg/ml, respectively.
† MTC was not measured in one patient.
CCH, C-cell hyperplasia; N+, nodal involvement.

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**Table 3** Histopathological findings in thyroid specimens from the 71 thyroidectomized MEN 2/FMTC gene carriers.

<table>
<thead>
<tr>
<th>Histopathological findings</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCH</td>
<td>55</td>
</tr>
<tr>
<td>Without MTC</td>
<td>5</td>
</tr>
<tr>
<td>Associated with MTC</td>
<td>50</td>
</tr>
<tr>
<td>MTC</td>
<td>66†</td>
</tr>
<tr>
<td>Size &lt;1 mm</td>
<td>4</td>
</tr>
<tr>
<td>Size 1–10 mm</td>
<td>54 (82%)</td>
</tr>
<tr>
<td>Size 10–40 mm</td>
<td>7</td>
</tr>
<tr>
<td>Bilateral</td>
<td>44</td>
</tr>
<tr>
<td>Unilateral</td>
<td>22</td>
</tr>
</tbody>
</table>

* Details of size relate to 65 MTC, as one tumour was not measured.
† Thyroid specimens from eight of these patients were not searched for CCH.
In a multivariate analysis, an older age was associated with advanced disease (MTC >10 mm, lymph node involvement) (Fig. 1b). Of the 61 patients who underwent lymph node surgery, 57 (93%) had no lymph node metastasis. Four patients (aged from 16 to 20 years) had unilateral nodal involvement. Table 4 shows the clinical, biological, and histological features of these four patients.

**Morbidity**

Two patients had transient hypoparathyroidism, and one patient had persistent hypoparathyroidism. No recurrent laryngeal nerve damage was observed.

**Follow-up**

After a mean follow-up of 4 years, 54 of the 71 patients (76%) were considered to be cured because their basal and pentagastrin-stimulated calcitonin concentrations were less than 10 pg/ml. Eleven patients (15.5%) had
Table 5 Clinical, biochemical and histological features in the six thyroidectomized MEN 2/FMTC gene carriers with either persistent or recurrent high basal or pentagastrin-stimulated calcitonin (CT) concentrations.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Preoperative CT concn (basal/peak*) (pg/ml)</th>
<th>Central nodal dissection</th>
<th>Cervicolateral nodal dissection</th>
<th>Lymph nodes (N+/-total)†</th>
<th>Histology</th>
<th>Postoperative CT concn (basal/peak) (pg/ml)</th>
<th>Follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMTC</td>
<td>F</td>
<td>15</td>
<td>19/215</td>
<td>+</td>
<td>Nd</td>
<td>0/5</td>
<td>Unilateral MTC, 2 mm Unilateral CCH Unilateral MTC, 1 mm Bilateral CCH Bilateral MTC, 4/4 mm No CCH Bilateral MTC, 7/1/3 mm Bilateral CCH Bilateral MTC, 15/10 mm Bilateral CCH Unilateral MTC, 6 mm Unilateral CCH</td>
<td>12/105 R</td>
<td>7</td>
</tr>
<tr>
<td>MEN 2A</td>
<td>M</td>
<td>13</td>
<td>14/190</td>
<td>Nd</td>
<td>Nd</td>
<td>Nd</td>
<td>Unilateral MTC, 12/13 mm Unilateral CCH Unilateral MTC, 12/13 mm Bilateral CCH Bilateral MTC, 15/10 mm Bilateral CCH Unilateral MTC, 6 mm Unilateral CCH</td>
<td>&lt;10/13 R</td>
<td>4</td>
</tr>
<tr>
<td>FMTC</td>
<td>M</td>
<td>15</td>
<td>21/153</td>
<td>Harvesting</td>
<td>Bilateral</td>
<td>0/33</td>
<td>Unilateral MTC, 2 mm Unilateral CCH Unilateral MTC, 1 mm Bilateral CCH Bilateral MTC, 4/4 mm No CCH Bilateral MTC, 7/1/3 mm Bilateral CCH Bilateral MTC, 15/10 mm Bilateral CCH Unilateral MTC, 6 mm Unilateral CCH</td>
<td>13/95 R</td>
<td>3</td>
</tr>
<tr>
<td>FMTC</td>
<td>F</td>
<td>16</td>
<td>137/1187</td>
<td>+</td>
<td>Unilateral</td>
<td>Central, 5/8</td>
<td>Unilateral MTC, 2 mm Unilateral CCH Unilateral MTC, 1 mm Bilateral CCH Bilateral MTC, 4/4 mm No CCH Bilateral MTC, 7/1/3 mm Bilateral CCH Bilateral MTC, 15/10 mm Bilateral CCH Unilateral MTC, 6 mm Unilateral CCH</td>
<td>30/1241 P</td>
<td>1</td>
</tr>
<tr>
<td>MEN 2A</td>
<td>F</td>
<td>20</td>
<td>710/11500</td>
<td>+</td>
<td>Bilateral</td>
<td>0/15</td>
<td>Unilateral MTC, 2 mm Unilateral CCH Unilateral MTC, 1 mm Bilateral CCH Bilateral MTC, 4/4 mm No CCH Bilateral MTC, 7/1/3 mm Bilateral CCH Bilateral MTC, 15/10 mm Bilateral CCH Unilateral MTC, 6 mm Unilateral CCH</td>
<td>39/780 P</td>
<td>4</td>
</tr>
<tr>
<td>MEN 2A</td>
<td>F</td>
<td>20</td>
<td>18/385</td>
<td>Nd</td>
<td>Bilateral harvesting</td>
<td>0/8</td>
<td>Unilateral MTC, 2 mm Unilateral CCH Unilateral MTC, 1 mm Bilateral CCH Bilateral MTC, 4/4 mm No CCH Bilateral MTC, 7/1/3 mm Bilateral CCH Bilateral MTC, 15/10 mm Bilateral CCH Unilateral MTC, 6 mm Unilateral CCH</td>
<td>8/43 P</td>
<td>6</td>
</tr>
</tbody>
</table>

CT was assayed as described in Methods, and normal ranges determined according to data from GETC (15, 16).

† No. involved/total examined.

F, female; M, male; Peak*, pentagastrin-stimulated CT peak; CCH, C-cell hyperplasia; Nd, not done; R, recurrent disease (postoperative pentagastrin testing was first normalized); P, persistent disease.
normal basal calcitonin concentrations, but no pentagastrin test was available. Six patients (8.5%), aged from 13 to 20 years, did not remain free of disease; two had an advanced staged disease: bilateral MTC (10 and 15 mm) in one case, and nodal metastases in the other case. The other four patients had an incomplete nodal dissection (n = 3), or had not undergone lymph node surgery (n = 1). Table 5 shows the clinical, biological, and histological features of these six patients.

Discussion
In our series, 71 gene carriers under 20 years of age, identified through familial genetic screening, were systematically evaluated for calcitonin concentration before thyroidectomy. We found high preoperative basal or pentagastrin-stimulated calcitonin concentrations in all of them; these were related to the presence of C-cell hyperplasia or MTC by histopathological examination of thyroid specimens. We demonstrated, as others have done (8, 13, 14, 18, 19), that surgery always reveals C-cell disease in thyroid specimens when basal calcitonin values are abnormal, and we showed that a significant relationship exists between basal calcitonin and stage of the disease in most patients. However, advanced disease may be present when basal calcitonin is still normal: among 17 patients with only an abnormal pentagastrin test, one had nodal metastases, another had a macroscopic MTC, and the patient with the lowest calcitonin peak (18 pg/ml) had bilateral and multifocal microscopic MTC. This suggests that thyroidectomy should obviously not be delayed until basal calcitonin concentrations are abnormal, because the disease is usually advanced at that time, and it should be proposed before the pentagastrin test becomes positive. Taking into account that MTC was already present when even the lowest calcitonin peak was registered, we consider that, in this population, calcitonin should not increase after pentagastrin testing. Provided that thyroidectomy is proposed as soon as pentagastrin-stimulated calcitonin is increased above the normal basal value (10 pg/ml), one may perform an early thyroidectomy and cure the patient.

Once gene carrier status is established, we suggest that thyroidectomy should be proposed while the patient is still at a young age, because an older age was associated with a worse histopathological stage and prognosis. Consensus about the need for thyroidectomy as early as at 1 year of age is well established for MEN 2B, for which the course of disease is worse and metastases are often present at the time of diagnosis (4, 20). For MEN 2A gene carriers, most authors have recommended that thyroidectomy be performed as early as 4–6 years of age (8, 11, 14, 21). In our series, the seven MEN 2A gene carriers younger than 6 years of age had bilateral or unilateral MTC. Thus, however young the age (two of our patients were 2 and 4 years old), MTC was already present, suggesting that age is not a reliable parameter on which to base a thyroidectomy. Thus, in order to operate for the disease in its early stages, thyroidectomy must be performed at least before the patient is 2 years of age.

The need for a systematic locoregional lymphadenectomy in addition to thyroidectomy is supported by the frequent finding that lymph node metastases are often associated with a macroscopic MTC (22, 23). Our data suggest that lymph node dissection is required to cure patients, even though the disease may be at an early stage, as was the case in our four patients with microscopic MTC but histologically proven lymph node metastases. Further in support of this, five of our six patients who were not surgically cured had either proven nodal metastases, or an incomplete cervical lymph node dissection, or had undergone no nodal surgery at all.

Although the risk of an advanced C-cell disease need not delay surgery, it is necessary to avoid laryngeal nerve damage and hypoparathyroidism, which are mainly due to the lymph node dissection associated with thyroidectomy. In our series, we observed no laryngeal morbidity, but hypoparathyroidism in 1.4% of patients. Surgical morbidity was previously reported to be the same in children of 5 years of age and in older patients (14, 24–26). The best procedure would be to refer to surgery those children who are both at the earliest stage of disease and old enough to have thyroidectomy without an increased morbidity. We thus suggest, first, that pentagastrin testing should be monitored from 2 years of age and, secondly, that thyroidectomy should be proposed as soon as pentagastrin-stimulated calcitonin concentrations increase to more than 10 pg/ml. Of course, to perform the procedure with the lowest morbidity, an experienced surgeon is required.

Several studies have reported the results of prophylactic thyroidectomy that was performed on patients on the basis of their gene carrier status, negative pentagastrin testing, or both (5, 9, 11, 13, 14, 24, 27). In our series, we consider that none of our patients had a true prophylactic thyroidectomy, as that must be defined by the lack of C-cell disease, rather than by the lack of biochemical features of the disease, which mainly depend on the sensitivity and ranges of the calcitonin assays used. Consequently, according to our experience, early rather than prophylactic surgery was performed in most of the previous studies, as C-cell disease was already present in the thyroid specimens analysed. This underscores the need to collect more data by using a sensitive calcitonin determination, in order to establish the long-term benefit of a truly prophylactic thyroidectomy in gene carriers with negative pentagastrin testing, in whom we should expect to remove histologically normal thyroid glands. The question then arises as to the necessity of systematically performing a lymph node dissection.

In conclusion, calcitonin determination through a sensitive immunometric assay plays an integral part in the management of MEN 2 gene carriers. The indication of thyroidectomy is undisputed when basal calcitonin is abnormal. When basal calcitonin is undetectable,
thyroid specimens. patients or providing histopathological examination of surgical procedure would require no nodal dissection, would become abnormal and whatever the age of the patient; such surgery would require no nodal dissection, would permit an early thyroidectomy and cure the patient. calcitonin greater than 10 pg/ml makes it possible to perform a pentagastrin-stimulated concentration of calcitonin greater than 10 pg/ml makes it possible to detect and whatever the age of the patient; calcitonin greater than 10 pg/ml makes it possible to detection of a pentagastrin-stimulated concentration of calcitonin greater than 10 pg/ml makes it possible to perform an early thyroidectomy and cure the patient. However, the best surgical procedure would be a true prophylactic thyroidectomy, before pentagastrin testing becomes abnormal and whatever the age of the patient; such surgery would require no nodal dissection, would cure children and have the least surgical morbidity.

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References


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