Characteristics of a Family with the MEN-2A Syndrome

Harm R. Haak
Arie C. Nieuwenhuijzen Kruseman

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This Article is brought to you for free and open access by Henry Ford Health System Scholarly Commons. It has been accepted for inclusion in Henry Ford Hospital Medical Journal by an authorized editor of Henry Ford Health System Scholarly Commons.
Results of screening and follow-up in a family with the MEN-2A syndrome are described. Fourteen (83%) subjects at risk were affected with medullary thyroid carcinoma (MTC). Asymptomatic pheochromocytoma and parathyroid hyperplasia were found in two instances each. Intrathyroidal MTC without metastases was found in the four youngest subjects and was associated with normal basal but abnormal pentagastrin-stimulated calcitonin (CT) levels. In the ten subjects with abnormal basal CT levels, metastatic spread to at least regional lymph nodes was found. In eight of these ten subjects, total thyroidectomy with excision of affected lymph nodes and additional radioiodine did not return CT levels to normal postoperatively. In the other two subjects, the CT levels returned to normal after thyroidectomy and an ablative dose of radioiodine, and remained normal during follow-up. This study confirms the view that family screening at a young age promotes the detection of MTC at a curable stage. Radioiodine as an adjunct to surgery may be of value in the prevention of tumor recurrence in patients with normal postoperative CT levels but residual thyroid tissue. (Henry Ford Hosp Med J 1987;35:104-6)

In 1980 we studied a newly discovered family with the MEN-2A syndrome. The index case was a 45-year-old woman (#6, Fig 1) with a locally invasive medullary thyroid carcinoma (MTC), but no signs or symptoms suggestive of hyperparathyroidism and/or pheochromocytoma. Her father had died at age 46 from a pheochromocytoma. A unilateral pheochromocytoma had been removed from her sister in 1969 at the age of 22. After total thyroidectomy, the patients with MTC received an ablative dose of $^{131}$I to irradiate normal, hyperplastic, and neoplastic C-cells adjacent to iodine-trapping follicular cells present in residual thyroid tissue (1).

The follow-up had two objectives: 1) to evaluate the prognostic value of basal and pentagastrin-stimulated calcitonin (CT) levels on the outcome of MTC, and 2) to evaluate the effects of $^{131}$I on residual MTC and on prevention of recurrence.

Patients and Methods

We studied 21 members of the pedigree shown in Fig 1 (patient #11 who lives in Canada where he had an operation for MTC is not included in our study group). Evaluation included a medical history, clinical examination, and measurement of basal CT (n < 14 pmol/L) and pentagastrin-stimulated CT (n < 40 pmol/L), carcinoembryonic antigen (CEA), calcium, phosphate, alkaline phosphatase in plasma, and 24-hour urinary excretion of VMA (1).

Total thyroidectomy was performed in those patients with abnormal basal and/or pentagastrin-stimulated CT levels. Cervical lymph nodes that appeared abnormal on palpation and macroscopic examination were resected. Two weeks after thyroidectomy, provocative testing with pentagastrin was repeated and a 24-hour uptake of a 1 mCi tracer dose of $^{131}$I and thyroid scan were performed. An ablative dose of $^{131}$I was administered orally with standard radiation precautions. Three months later, thyroid replacement was withdrawn for four weeks, and the thyroid scan with a tracer dose of 1 mCi $^{131}$I was repeated. The evaluation was repeated at that time and at yearly intervals.

Results

The pedigree is given in Fig 1. Apart from the index case (#6), 14 (83%) of the family members at risk had MTC at first screening, although none had presented clinically. In our studies abnormal CT levels were found in five of seven siblings of the index patient and eight of nine members of the next generation. Nine of these 13 individuals (mean age 28, range 13 to 43) had raised basal CT levels, and four (mean age 9.5, range nine to 11 years) had elevated levels only after pentagastrin stimulation. The CEA level was abnormal in six of the nine patients with elevated basal CT levels. In all cases the MTC was multicentric, and all patients with increased basal CT levels had lymph node involvement. Postoperative basal and pentagastrin-stimulated CT levels became normal in two of nine patients with preoperatively abnormal basal CT levels and in all four patients with preoperatively abnormal pentagastrin-stimulated CT levels only (Fig 2). After thyroidectomy, residual thyroid tissue was demonstrated by $^{131}$I uptake in all patients, and therefore all received an ablative dose of $^{131}$I (50 to 75 mCi $^{131}$I sodium iodide) in an attempt to destroy normal and abnormal C-cells adjacent to follicular cells in the residual thyroid tissue.

The results of investigations to detect parathyroid and adrenal abnormalities were normal at first presentation. Nevertheless,
parathyroid enlargement was found in two patients during thyroideotomy. The results of microscopy of the removed parathyroids were consistent with hyperplasia.

**Follow-up**

In all but one of the patients whose CT levels were elevated postoperatively, the CT levels remained elevated during follow-up (Fig 3). The exception was the index patient (#6, Fig 1) in whom CT and CEA levels gradually decreased to the normal range. In the patients whose basal and pentagastrin-stimulated CT levels were normal postoperatively, these levels remained within the normal range (Fig 3), with the exception of patient #20 (Fig 1), whose last basal CT value was slightly elevated (21 pmol/L) but whose pentagastrin-stimulated CT level was normal. None of the operated patients has had any clinical sign of residual or recurrent MTC.

Recently, abdominal computed tomography was performed in patients #6, #8, #9, and #13. These patients had normal urinary excretion of VMA and no symptoms suggestive for pheochromocytoma except for patient #9 who presented with atypical paroxysms but normal blood pressure.

In two of these patients, computed tomography revealed a unilateral (patient #6) and bilateral (patient #9) pheochromocytoma. The presence of pheochromocytomas was further substantiated by elevated plasma catecholamine levels nonsuppressible after clonidine (2) and positive meta-iodo-benzylguanidine (MIBG) scans. Patient #9 underwent a bilateral adrenalectomy after which the paroxysms subsided. Patient #6 refused adrenalectomy because of the absence of symptoms related to pheochromocytoma.

**Discussion**

Our experience confirms the generally accepted view (3-5) that screening in MEN-2 family members at a young age promotes the identification of early MTC at a curable stage. An abnormal basal CT level according to our assay criteria suggests metastases to at least the regional lymph nodes. A normal basal but abnormal pentagastrin-stimulated CT level suggests intrathyroidal disease which has not yet metastasized.

The observation of metastases in at least regional lymph nodes in young subjects with only moderate increases of basal CT levels and no palpable disease agrees with many other reports that early metastatic spread is common (6,7). In most of

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**Fig 1**—Pedigree.

**Fig 2**—Basal and peak pentagastrin-stimulated CT values before surgery at listed ages. (Solid circles represent individuals whose stimulated CT levels became normal postoperatively. Open circles indicate those who had elevated values postoperatively.)

**Fig 3**—Serial basal and peak pentagastrin-stimulated CT values postoperatively and during follow-up after ^131^I was administered shortly after the postoperative testing.
these patients the CT levels remained abnormal after total thy­
roidectomy and excision of affected lymph nodes, which might
imply that our surgical procedure was inadequate for cure. Be­
cause of similar experiences in other studies (6,7), we recom­
mend total thyroidectomy plus at least regional lymphadene­
tomy with modified radical lymph node dissection at the site of
macroscopic metastases. However, in many cases this procedure
is also not curative.

Since C-cells do not trap iodine, radioiodine treatment is not a
usual adjunct to surgery in the management of residual sporadic
and hereditary MTC (1,6). However, since normal and probably
also hyperplastic C-cells are very sensitive to radiation from ^I
accumulated in adjacent follicular cells (7), and since total thy­
roidectomy is virtually always incomplete, radioiodine may
help prevent the development of MTC from residual C-cells. In
the family presented here, no clinical tumor recurrence has been
found during a follow-up period of seven years, whereas in other
series tumor recurrences after complete thyroidectomy alone
have been reported (6,7). Longer follow-up data are clearly
necessary before we conclude that radioiodine is indeed useful
as an adjunct to surgery in patients who also have normal
postoperative CT levels but scintigraphically identified residual
thyroid tissue.

Pheochromocytoma in MEN-2A patients usually presents insidiously and is difficult to detect at an early stage. We identified
two patients with pheochromocytomas who did not have typical
clinical symptoms or elevated urinary excretions of VMA. More
advanced biochemical and radiological techniques are
warranted before one can conclude that pheochromocytoma
is absent.

References

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"Communication is the Cape Canaveral of the scholar. The product of
curiosity must be launched from the pad or it serves no purpose."

George A. Perera