Henry Ford Hospital Medical Journal

Volume 40 | Number 3 Article 25

9-1992

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Results of follow-up studies in four large multiple endocrine neoplasia type 2A families (total of 95 patients affected) have shown a positive effect on the course of the disease since early screening and intervention were initiated in 1974. (Henry Ford Hosp Med J 1992;40:256-7)

The multiple endocrine neoplasia type 2 (MEN 2) syndrome is an autosomal dominant inherited disease characterized by medullary thyroid carcinoma (MTC) and in many cases pheochromocytoma. In the present study we evaluated the clinical findings in four large families.

Patients and Methods

Since 1974, four large MEN 2 families with a total of 350 members have been examined annually. The screening procedure involves measurement of plasma calcitonin (CT) levels before and after provocation with calcium (2.5 mg/kg intravenously) and of 24-hour excretion of catecholamines and metabolites.

Results

In these four families, 96 patients with MEN 2 have been identified. A total of 39 patients have died from MEN 2-related causes at a mean age of 48 years, most of them (31 individuals) before 1975. Fifteen of these 39 patients died from extensive metastases from MTC and 24 died from consequences of pheochromocytomas (Tables 1 and 2). Thirty-one of the patients died prior to the 1975 onset of periodic screening of families (Table 1). The screening efforts have resulted in identification of 65 patients with MTC. Of 14 known to be affected prior to screening (symptomatic group in Table 3), six are alive and six have died of the disease. During the first screening 39 additional patients were identified; only 13 patients have normal test results currently but all are alive. Twelve patients converted from normal to positive CT results, eight were cured by thyroidectomy, and one patient has recurrent disease. Three patients with positive CT results are scheduled for surgery (Table 3).

The clinical data are given in the four pedigrees in Figs 1 and 2 and in Tables 1 through 4.

Table 1
Natural History of MEN 2 Patients Dying Before 1975

Family	Patients (n)	Died From MEN 2	Mean Age (Years)	Cause of Death MTC	Cause of Death Pheo	Alive in 1975
I	33	9	53	4	5	24
II	25	12	43	2	10	13
III	22	7	42	2	5	15
IV	16	3	47	2	1	13
Total	96	31	46	10	21	65

Discussion

An analysis of the results permits several conclusions. Since screening for MTC was started, five patients have died of extensive metastases of MTC (Table 2). After surgery, most converters remain negative. The long-term prognosis of C-cell hyperplasia (CCH) is favorable. MTCs generally develop earlier than pheochromocytomas. Symptomatic hereditary MTCs have the same prognosis as sporadic forms (1). The results support the conclusion that identification of patients with stage I disease (intrathyroidal MTC with no metastases) has a positive impact on clinical outcome (2). The outcome in stage II (MTC with movable cervical metastases), stage III (local invasion with fixed cervical nodes), and stage IV (distant metastases) is similar (2). The clinical course in patients with CCH is particularly favorable.

The effects on survival of patients with pheochromocytomas have been remarkable. Since 1975, none of the patients has died of pheochromocytoma and no metastases of pheochromocytomas were observed (Table 4). Pheochromocytomas frequently occur in accessory adrenal glands. Rarely, pheochromocytomas may develop earlier than MTC. The decision to perform unilat-

Submitted for publication: November 21, 1991.
Accepted for publication: January 27, 1992.
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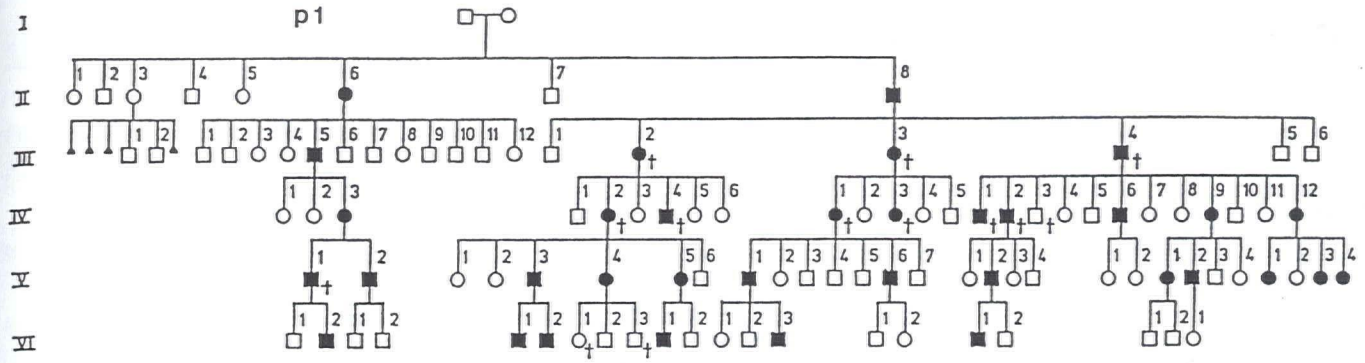

Fig 1—Pedigree of the largest MEN 2A family. Solid squares = affected males; solid circles = affected females.

Table 2
Patients Treated for the MEN 2 Syndrome Since 1974

Family	Patients (n)	Died From MEN 2*	Mean Age (Years)	Cause of Death MTC	Cause of Death Pheo	Alive in 1992
I	24	4	54	3†	1‡	19
II	13	2	45	2§	—	11
III	15	2	63	—	2#	12
IV	13	—	—	—	—	13
Total	65	8	54	5	3	55

*Two MEN 2 patients died from a myocardial infarction at 71 and 76 years of age.
†At ages 38 and 74 (females) and 48 (male).
‡At age 57 (female) before family study could be completed.
§At ages 22 (female) and 70 (male).
#At ages 51 and 74 (females) before family study could be completed.

Table 3
Patients Treated for Medullary Thyroid Carcinoma

Family	Patients (n)*	Sympto-matic†	Call-up†	Converters†	Operated On MTC/CCH	Not Operated
I	24*	3 (0)	16 (4)	5 (2)	21	3‡
II	13	4 (0)	6 (1)	3 (3)	12	1§
III	15	4 (1)	9 (4)	2 (1)	11	2‡,§
IV	13	3 (1)	8 (5)	2 (2)	13	—
Total	65	14 (2)	39 (14)	12 (8)	57	6

*One patient operated on for pheochromocytoma had no signs of medullary thyroid carcinoma (MTC).
†Data in parentheses indicate number of patients operated on for MTC or C-cell hyperplasia (CCH) and cured.
‡Surgery being scheduled.
§Not operated on for MTC for religious reasons.

eral or bilateral adrenalectomy for pheochromocytomas has been made on a case-by-case basis.

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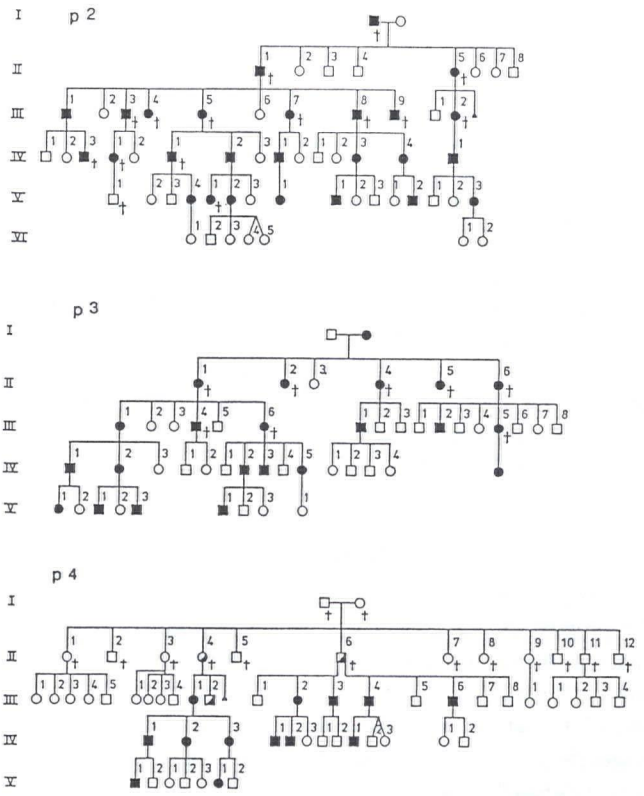

Fig 2—Pedigree of the 2nd, 3rd, and 4th MEN 2A families. Solid squares = affected males; solid circles = affected females.

Table 4
Patients Treated for Pheochromocytomas Since 1974

Family	Patients	MTC	Pheochromocytoma	Bilateral	Unilateral	Accessory
I	24	21	12	11	1	5
II	13	12	8	8	—	3
III	15	11	4	2	2	1
IV	13	13	4	1	3	2
Total	65	57	28	22	6	11