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Multiple Endocrine Neoplasia Type 2A: A Northern Ireland and Australian Family

David R. Hadden,* Fergus O’Reilly, Laurence Kennedy, and Colin Russell

A Northern Ireland/Australian family with multiple endocrine neoplasia type 2A is described. Three members of the first generation studied have died, two men (aged 35 and 51) as a result of metastatic medullary thyroid carcinoma and one woman (the index case, aged 50) due to hypertensive complications during thyroidectomy from an undiagnosed pheochromocytoma. All members of this family found by screening to have either medullary thyroid carcinoma or pheochromocytoma, or both, have been asymptomatic for their disease. (Henry Ford Hosp Med J 1987;35:107-9)

Medullary thyroid carcinoma (MTC) in association with pheochromocytoma was first described by Sipple (1), although earlier cases have been identified retrospectively (2). The hereditary nature was recognized by Cushman (3), and many families have since been described (4-6), including the families reported at the First International Workshop on Multiple Endocrine Neoplasia Type 2 (MEN-2) Syndromes in 1984.† All reports are consistent with autosomal dominant inheritance with a high degree of penetrance. The age of presentation varies, and Ponder (7) has suggested that some individuals who inherit the gene will not present clinically with thyroid tumors until a late age. All members of these families are therefore at risk and screening is essential.

The G-kindred have been living in County Antrim, Northern Ireland, for many generations. Several members emigrated to Australia in their youth. The occurrence of several cases of MTC and pheochromocytoma over a period of years, and the chance meeting of surgical colleagues, brought the familial nature of the condition to light, although the separate branches of the family had not connected their problems over the years.

The initial screening procedure used in this study was measurement of basal unstimulated plasma calcitonin (CT) and 24-hour urinary catecholamines, followed by adrenal computed tomography and 131I-meta-iodo-benzylguanidine (MIBG) imaging in several members. The pedigree is shown in the Figure.

Case Reports

The ages of the patients in the following case reports are from 1981 unless otherwise stated.

Case II-1

The index case of the kindred is a 50-year-old woman who was admitted to her local hospital in 1972 for surgical removal of a solitary thyroid nodule. Plasma CT was not measured. During surgery she became acutely hypertensive and developed cardiac dysrhythmias. Immediately postoperatively, cardiac arrest occurred and the patient died. Autopsy showed multifocal MTC without secondary deposits and a right adrenal pheochromocytoma. No abnormality was noted in the left adrenal gland.

Case II-2

A 61-year-old man was found on clinical screening of relatives of case III-3 to have a palpable thyroid gland. Plasma CT was 31.0 μg/L (normal < 0.08 μg/L). His blood pressure was normal, but 24-hour urinary catecholamines showed the adrenaline fraction to be elevated on several occasions, the highest level being 213 nmol/24 hours (adult range 3 to 109 nmol). 131I-MIBG imaging showed bilateral adrenal tumors, although adrenal computed tomography results were inconclusive. Bilateral adrenalectomy was performed and at least two separate pheochromocytomas were identified in the right adrenal gland.
and a number of small tumor nodules in the left adrenal gland. Three months later, total thyroidectomy was performed and bilateral nodules of multifocal MTC were identified.

Case II-3
This man was one of three brothers who had emigrated from Northern Ireland to Australia. He died in Adelaide in 1960, at the age of 36. Limited autopsy was performed and while no official report is available, his brother remembers that the doctor was "very interested in his thyroid" (personal communication, Mr. A.J. Edis). It is probable that he had MTC; he may also have had a pheochromocytoma.

Case II-4
This patient was a 57-year-old man, who was another of the three brothers who had emigrated to Australia. When his younger brother was diagnosed as having MTC, he was found to have a high basal CT level which increased on calcium infusion. He also had an elevated plasma parathyroid hormone without significant hypercalcemia. Total thyroidectomy was performed in 1981, and histology confirmed multiple foci of MTC, with a metastatic deposit in the paratracheal region (personal communication, Mr. A.J. Edis).

Case II-5
This patient, the youngest of three brothers who emigrated to Australia, was a 50-year-old man who at thyroidectomy in 1981 was found to have undifferentiated MTC (personal communication, Mr. A.J. Edis). Metastases were disseminated throughout his skeleton, and he subsequently died.

Case III-3
A 35-year-old woman was found on clinical examination to have a large multinodular firm goiter. Basal plasma CT was 67.8 μg/L. Her blood pressure was normal, and 24-hour urinary catecholamine levels were not elevated. Total thyroidectomy was performed and the diagnosis of MTC confirmed. Five months postoperatively, plasma CT dropped to an undetectable level (< 0.08 μg/L).

Case III-6
A 29-year-old woman was found on clinical examination to have a small smooth goiter. Basal plasma CT was 20.9 μg/L; '99technetium thyroid scan showed one small "cold" area in each lobe of the thyroid, and computed tomography showed defects in the lower pole of each lobe of the thyroid. Total thyroidectomy was performed and multiple tumor nodules of MTC were found. Three months postoperatively, the plasma CT had dropped to < 0.08 μg/L. Her blood pressure was normal, and basal urinary catecholamine levels were not elevated. Clonidine stimulation test results were normal and '125I-MIBG was negative. The initial adrenal computed tomography showed a small nodule in the left adrenal, and she subsequently had successful removal of bilateral pheochromocytomas.

Case III-7
A 25-year-old man had a barely palpable thyroid gland and no clinical symptoms. Basal plasma CT was 0.71 μg/L, which remained elevated on subsequent measurement. He was at first unwilling to have neck surgery. Computed tomography of the adrenals subsequently showed bilateral nodules consistent with pheochromocytomas, although plasma and urinary catecholamine levels were normal. Adrenal and thyroid surgery is planned.

Case III-8
A 34-year-old man was found on screening to have an elevated basal plasma CT level (13.6 μg/L). On examination he had a firm nodular thyroid gland. His blood pressure was normal, and 24-hour urinary catecholamines were in the normal adult range. '125I-MIBG scanning of the adrenal medulla was consistent with bilateral hyperplasia, and computed tomography showed bilateral nodules. Bilateral adrenalectomy was performed and the presence of multifocal pheochromocytomas confirmed. Subsequent total thyroidectomy confirmed the presence of MTC.

Case III-14
A 22-year-old man was found on screening to have a marginally elevated basal plasma CT level (0.62 μg/L). Clinically he was euthyroid, and the thyroid gland was barely palpable. His blood pressure was normal, 24-hour urinary catecholamine levels were not elevated, and computed tomography of the adrenals was normal. Total thyroidectomy was performed, and histological examination showed the presence of multiple tumor nodules of MTC.

Normal unstimulated levels of plasma CT have been found in several other family members (cases III-1, III-5, III-9, and III-13, and IV-1, IV-2, IV-3, and IV-11). These family members are mainly young children, and the use of pentagastrin-stimulation tests in addition to annual unstimulated screening will be kept carefully under consideration, as discussed in several other papers presented at this workshop.

Marginally elevated plasma CT levels (unstimulated) have been found in cases III-2, III-15, IV-4, IV-5, and IV-6. These members will be kept under observation, although the problems of surveillance and compliance are well recognized and the optimum time for surgical intervention remains uncertain. No further investigations for pheochromocytoma have been undertaken to date.

Patients III-10 and III-11 were both found on screening to have MTC and have had total thyroidectomy (personal communication, Mr. A.J. Edis). Patient III-10 also had a 1.2 cm adenoma of the right inferior parathyroid gland, with biochemical evidence of mild hyperparathyroidism. Patient II-6 had removal of a thyroid tumor in 1961 which has retrospectively been reclassified as MTC. She remains well.

Discussion
Many aspects of the screening, diagnosis, and management of patients with this syndrome, and the management of other family members, were discussed at the Second International Workshop on MEN-2. Between 1965 and 1978, 14 cases of MTC were diagnosed histologically in Northern Ireland (population 1.5 million). Only one of these was a member of this family, and she was the index case who had died of the unrecognized pheochromocytoma (8).

While it is essential that each person in a kindred be seen and investigated as a private individual, the possession of an inherited trait involves discussion of known disease and treatments in other relatives. This is more difficult in a relatively close-knit community than when family members are widely scattered. We attempted to bring together many of the members of this kindred for counseling and screening on the same day, but quickly found that this was inadvisable, not only because of various family interactions but also because of the reasonable desire for personal discussion.

Although the risk of death from MTC and the effect of early detection and early thyroidectomy are both becoming better cat-
egorized (9), in the MEN-2 syndromes pheochromocytoma may actually produce a greater risk of death, especially in young adulthood and in childbirth (10). Three of our cases (II-2, III-6, and III-8), despite the presence of bilateral pheochromocytomas, had normal pressures and were asymptomatic without elevation of urinary catecholamines. Hereditary pheochromocytomas appear unique in this respect (11). Data from families studied in The Netherlands (6) showed that the chance is very small that a MEN-2A patient with a pheochromocytoma will die as a result of a malignant change with metastases of this tumor. However, the devastating metabolic effects of an undiagnosed and untreated pheochromocytoma, as shown by the index case and the similar experience of others (4), has led us to adopt a radical surgical approach to the adrenal gland. van Heerden et al (12) favor bilateral adrenalectomy in patients with elevated catecholamines even if only one adrenal gland is affected macroscopically. Others take a more conservative approach (13). Symptoms of headache, inappropriate or excessive sweating, or palpitations with associated hypertension are rarely manifest (as in this family), and therefore some form of screening is mandatory.

The natural history of pheochromocytoma is difficult to document, and diagnosis is often precipitate (14). The traditional screening test of 24-hour urinary catecholamine levels may not be of any use in the early stages when secretion may be intermittent. MTC itself may even be the best marker for these hereditary pheochromocytomas. Adrenal venous sampling is highly selective but invasive, and has largely been superseded by computed tomography. The use of 131I-MIBG to identify these tumors is more helpful in the established case (15), particularly if metastases are suspected (16). A submaximal exercise test may turn out to be a useful screening procedure with measurement of plasma catecholamines (10), but the long survival of some members of our kindred with known pheochromocytoma suggests that in some cases these adrenal tumors may be inactive during normal life. The stress of anesthesia, surgery, or childbirth is well known to activate a previously slumbering pheochromocytoma, as observed with the death of our index case and probably the unexplained sudden death during operation of Case II-3.

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References