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ENDOCRINOLOGY, METABOLISM AND DIABETES

Multiple endocrine neoplasia type 2A in a black South African family

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The genetic abnormality of multiple endocrine neoplasia type 2A (MEN 2A) has recently been elucidated. Over 95% of families with MEN 2A have an identifiable mutation of the RET proto-oncogene on chromosome 10. This report describes a black South African woman with MEN 2A in whom a mutation of the RET proto-oncogene was identified. Current genetic knowledge and recent changes in clinical practice are presented, with specific reference to the other family members found to be carrying the mutant RET gene.

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Multiple endocrine neoplasia type 2A (MEN 2A) is a genetically determined disease characterised by medullary carcinoma of the thyroid, phaeochromocytoma and hyperparathyroidism (hyperplasia or adenoma). MEN type 2B (MEN 2B) is characterised by medullary carcinoma of the thyroid, phaeochromocytoma, mucosal ganglioneuromas and a marfanoid habitus. MEN 2A and B, together with familial medullary carcinoma of the thyroid, are inherited as autosomal dominant conditions. The genetic defects responsible for these conditions have recently been identified. Linkage analysis in the late 1980s mapped the defect to the pericentromeric region of chromosome 10 for MEN 2A, 2B and familial medullary carcinoma of the thyroid.[1] In 1993 specific missense mutations of the RET proto-oncogene were identified.[2,3]

This report describes a black South African family with MEN 2A in whom the specific genetic defect has been identified.

Index case

A 29-year-old woman was admitted to Baragwanath Hospital in October 1994. She complained of episodes of headache, sweating, palpitations, epigastric pain, dizziness and weight loss, all of recent onset. Hypertension had been diagnosed earlier in the same year while she was pregnant. This had been her first pregnancy, and had ended in a stillbirth near term. She had had a thyroid swelling for about 12 years; her mother and sister had apparently died of thyroid disease.

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Examination revealed a young woman with a large asymmetrical goitre of hard consistency. Twenty-four-hour ambulatory blood pressure monitoring showed maximum systolic and diastolic blood pressures of 199 and 125 mmHg, respectively; the minimum systolic and diastolic blood pressures were 105 and 61 mmHg respectively. The maximum recorded heart rate was 140/min (sinus rhythm). There was echocardiographic evidence of left ventricular hypertrophy. The urea and electrolyte values, blood glucose level, thyroid functions, serum calcium and parathyroid hormone levels were all normal. The 24-hour urinary vanillyl mandelic acid level was elevated at 55.2 µmol (normal < 35). Computed tomography showed a mass in the region of the left adrenal gland that manifested increased uptake on a meta-iodobenzylguanidine isotope scan. Evidence of medullary carcinoma was found on fine-needle aspirate of the thyroid.

The patient was stabilised for 10 days on prazosin 1 mg 8-hourly, atenolol 50 mg once daily and long-acting nifedipine 60 mg once daily. A left adrenal phaeochromocytoma was removed. Biopsies of numerous small white nodules on the liver surface revealed metastatic medullary carcinoma. The patient had an uneventful postoperative course; she declined surgery to the thyroid gland. A year later, following comprehensive genetic counselling, she had an uncomplicated pregnancy and delivered a normal male infant by caesarean section. After this, she underwent sterilisation.

Genetics

Blood for genetic studies was obtained from the index case and 8 other family members. None of the members of the patient's family showed any clinical evidence of phaeochromocytoma, thyroid malignancy or hyperparathyroidism. The genetic studies, performed by Dr Robert McMahon, clinical molecular geneticist, East Anglian Medical Genetics Service, Molecular Genetics Laboratory, Addenbrooke Hospital, Cambridge, UK, identified a missense mutation in codon 634 of exon 11 of the RET gene. Three members of the family were shown to be carrying the mutant RET gene (Fig. 1): the index patient

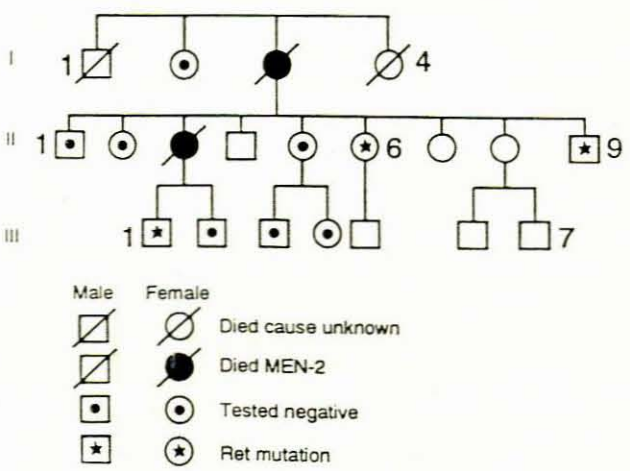

Fig. 1. Family tree of index case.

(generation II, number 6), one of her brothers (23 years; generation II, number 9) and a nephew (18 years; generation III, number 1).

Discussion

Analysis of the RET gene sequence allowed prediction of the structure of the protein coded for by this gene. This protein shares numerous sequences with transmembrane tyrosine kinase receptors;[4,5] the ligand that binds to the RET-encoded receptor is unknown. Missense mutations in the gene result in amino acid changes in the protein, which in turn alter the receptor's performance. The mutations described in MEN 2A result in amino acid substitutions in the extracellular cysteine-rich domain of the receptor. The mutation of codon 634 found in this family results in receptor dimerisation, mimicking the effect caused by the binding of a ligand.[6] Activation of the receptor results in cellular changes that cause uncontrolled growth and replication. Because only a single mutant allele of the RET gene results in neoplastic transformation, MEN 2A is inherited in an autosomal dominant way. The receptor tyrosine kinase encoded by the RET gene is expressed in derivatives of neural crest cells, including neural crest-derived tumours such as medullary carcinoma of the thyroid and phaeochromocytoma.

The identification of a specific genetic defect in MEN 2 has a number of clinical implications. Previously every family member would have had annual biochemical screening from 6 years of age, which includes plasma calcitonin assays for medullary carcinoma of the thyroid, both baseline and stimulated (pentagastrin and calcium). These tests may produce false-positive or equivocal results and induce unpleasant side-effects.

Genetic analysis and identification of mutant genes allow prophylaxis of medullary carcinoma of the thyroid. Early thyroidectomy in patients aged 4 - 5 years, without any biochemical testing, would be justified.[7] The reasons for early thyroidectomy include documented carcinoma in young patients,[8] some as young as 6 years old,[9] and a penetrance approaching 100% by the age of 30 years,[10] as measured by pentagastrin stimulation testing.[11] Family members who do not carry the mutant gene need no further tests. In this regard, the index patient's son will require genetic testing by the age of 5 years. The other two affected relatives declined prophylactic thyroidectomy at this stage.

In MEN 2A phaeochromocytoma develops in over 50% of affected patients, and hyperparathyroidism in 30%.[6] Phaeochromocytomas manifest, on average, 10 years after the development of medullary cell hyperplasia. Following thyroidectomy, screening for phaeochromocytoma would need to be continued, as would periodic calcium assays for hyperparathyroidism.

This report on a black South African family with MEN 2A describes a specific RET mutation causing this disease. A Medline search failed to find any reference to RET mutations in black South Africans. Current genetic knowledge and recent changes in clinical practice are presented.

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