MULTIPLE ENDOCRINE NEOPLASIA TYPE 2B

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Introduction

Multiple endocrine neoplasia type 2 (MEN 2) is a distinct hereditary syndrome that has an autosomal pattern of inheritance (OMIM 2005). There have been 500–1000 MEN 2 kindreds reported in the literature. The MEN 2 syndrome consists of three variants: MEN 2A, MEN 2B and familial medullary thyroid cancer (Table 1). Patients with MEN 2B develop medullary thyroid cancer (100%), pheochromocytoma, mucocutaneous neuromas and have characteristic physical features. MEN 2B accounts for 5–10% of MEN 2 cases. In patients with MEN 2B, neuromas may involve the skin, musculoskeletal system, gastrointestinal tract and eyes (Schimke et al. 1968, Williams and Pollock 1966a).

Patients with MEN 2B often develop aggressive medullary thyroid cancer within the first decade of life. Although MEN 2B is uncommon, early genetic screening and diagnosis offers the only chance at curative treatment. Because the penetrance of MEN 2B is 100%, clinical awareness of this syndrome and its physical manifestation is essential. Genetic screening identifies 95–99% of gene carriers at risk of developing MEN 2. This has resulted in prophylactic treatment of gene carriers who have no clinical evidence of disease and has improved patient outcome (Kebebew et al. 2000).

In this chapter, we review the clinical manifestation, pathogenesis, and management of MEN 2B. We also review the common physical and neurocutaneous findings that can be used to identify affected or at-risk patients before they develop medullary thyroid cancer and pheochromocytoma.

Historical perspective and Terminology

The MEN 2 syndrome was originally described by Sipple (1961), who reported an association of pheochromocytoma with medullary thyroid carcinoma. **John H. Sipple** was born in 1930 in Lakewood, Ohio and graduated from Cornell University Medical College in 1955. He trained in internal medicine at the State University of New York Medical Center (SUNY) in Syracuse. He then did a fellowship in pulmonary medicine at the Johns Hopkins Hospital in Baltimore, Maryland. In 1962 he returned to Syracuse to practice Pulmonary and Internal Medicine, and was appointed clinical professor of medicine at SUNY Medical Center in 1977. Dr. Sipple became a governor of the Upstate New York region of the American College of Physicians and president of the Internist Associates of Central New York (Who named it? 2007).

The triad of medullary thyroid carcinoma, pheochromocytoma, and parathyroid hyperplasia or adenoma, in association with elevated calcitonin and catecholamine levels (MEN 2A) was originally known as Sipple's syndrome (Boord 2004). Another eponym for MEN 2 is Wagenmann-Froboese syndrome (OMIM 2005). Wageman (1922) and Froboese (1923) described in part a clinical syndrome of multiple mucosal neuromas, pheochromocytoma, medullary carcinoma of the thyroid, and asthenic body build with muscle wasting of the extremities (marfanoid habitus). Williams and Pollock (1966) further characterized this MEN 2B phenotype with a description of true mucosal neuromas, intestinal ganglioneuromatosis, pheochromocytoma, and medullary thyroid carcinoma (Boord 2004, Gorlin et al. 2001) in two unrelated patients (OMIM 2005). The father of one of the

Table 1. The MEN 2 syndrome and its variants and affected sites

MEN 2 syndrome variants	Affected sites
MEN 2A	Families with medullary thyroid cancer, parathyroid disease, or both; rarely some families may have cutaneous lichen amyloidosis
MEN 2A (1)	Families with medullary thyroid cancer and pheochromocytoma, parathyroid disease, or both
MEN 2A (2)	Families with medullary thyroid cancer and pheochromocytoma in at least one member; objective evidence against the presence of parathyroid disease in affected and at-risk members
MEN 2A (3)	Families with medullary thyroid cancer and parathyroid disease in at least one member; objective evidence against the presence of pheochromocytoma in affected and at-risk members
MEN 2B	Families with medullary thyroid cancer, pheochromocytoma, mucosal neuromas, musculoskeletal abnormalities usually without parathyroid disease
Familial medullary thyroid cancer (FMTC)	Only medullary thyroid cancer; families with at least four members with medullary thyroid cancer and no objective evidence of pheochromocytoma or parathyroid disease on screening of affected and at-risk members
Other	Families with fewer than four members with medullary thyroid cancer but none with pheochromocytoma or parathyroid disease on biochemical screening or families with clinical screening results that could not be confirmed

patients had very thick lips and eyelids, and tongue lesions as did his daughters. He also had medullary thyroid cancer and died at 38 years old after an abdominal operation, having had symptoms suggestive of a pheochromocytoma (OMIM 2007, Williams and Pollock 1966). Other eponyms for MEN 2B are MEN type 3, Mucosal neuromata with endocrine tumours, Mucosal Neuroma syndrome, Wagenmann-Froboese syndrome, or Ganglioneuromatosis of the alimentary tract (OMIM 2007).

Incidence and prevalence

The precise incidence and prevalence of MEN 2 is unknown. Based on the National Cancer Institute's Surveillance, Epidemiology and End Result program, the age-adjusted annual incidence of medullary thyroid cancer in the United States ranges from 0.1 to 1.6 cases per million (NCI 2005). Because MEN 2B accounts for 5–10% of all MEN 2 cases and MEN 2 accounts for 25% of all medullary thyroid cancer cases, the estimated annual age-adjusted incidence is 4 cases per 100 million. The prevalence of thyroid cancer in the United States is 0.1%; therefore, the estimated prevalence of MEN 2B is 0.0025%.

Clinical manifestations of MEN 2B

Neurocutaneous and physical manifestations

Although medullary thyroid cancer and pheochromocytoma account for most of the morbidity and mortality associated with MEN 2B, the neurocutaneous manifestations and non-endocrine physical findings are important in identifying at-risk individuals early in life. Moreover, some of these physical

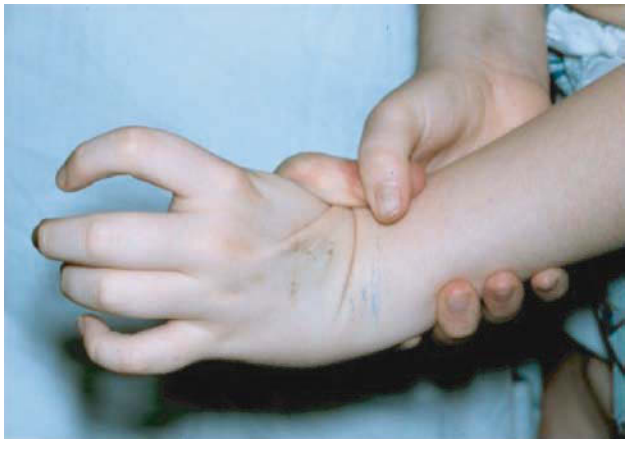


Fig. 1. A 11 year-old boy with MEN 2B demonstrates laxity in his first metacarpal joint with complete hyperextension causing no pain.

features contribute greatly to the poor quality of life that these patients endure (O'Riordain et al. 1995).

Patients with MEN 2B are often described as having a marfinoid body habitus with a tall and thin frame, disproportionately long limbs, joint laxity and severe muscular wasting (Fig. 1) (O'Riordain et al. 1995). Weakness especially of the proximal muscles of the extremities seen in 15% simulates a myopathic state. In infancy, there is often a history of profound difficulty in feeding with failure to thrive. The distinct facies is elongated and characterized by a wide-eyed expression, broad-base nose, and large nodular lips with submucosal nodules on the vermilion border (Gorlin et al. 2001). Some patients with MEN 2B will also have thickened lips and eyelids, the latter resulting in eversion of the upper eyelids. Surgical resection of the lips reveals enormous enlargement of the diameter of the peripheral nerves. The lower face appears long. Circumoral and midfacial lentiginosis have been occasionally seen. Slit-lamp examination often reveals corneal nerve thickening with medullated nerve fibers (O'Riordain et al. 1995).

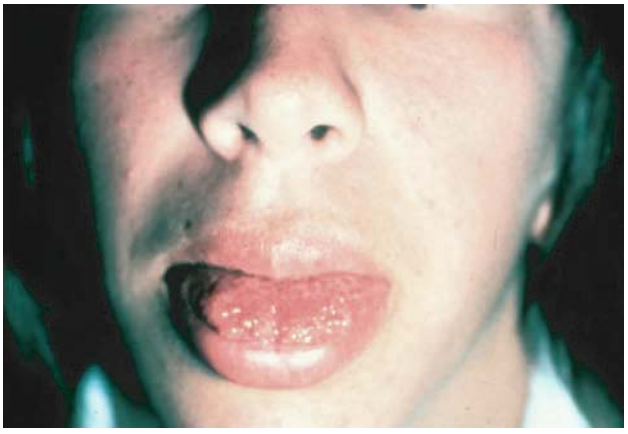
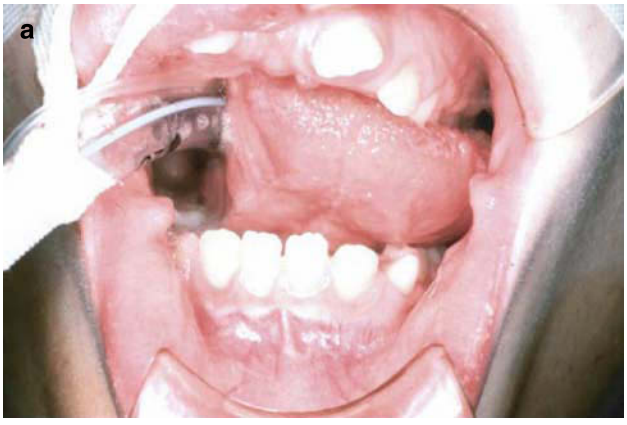


Fig. 3. Mucosal neuroma in the anterior tongue in a patient with MEN 2B.



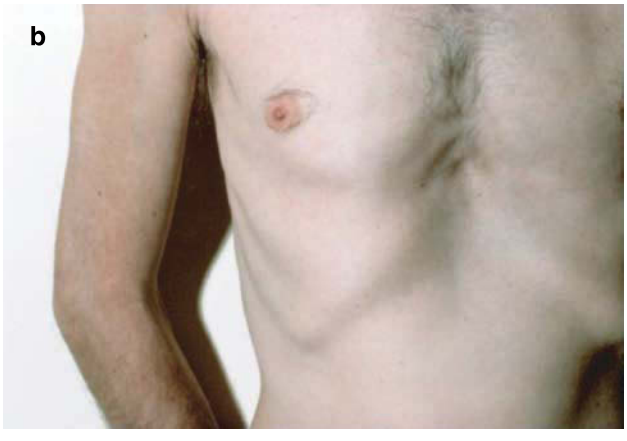


Fig. 2. (**a**) Abnormal dentition in a young girl with MEN 2B about to undergo total thyroidectomy and lymph node dissection for her medullary thyroid cancer, and (**b**) Pectus excavatum in a patient with MEN 2B.

Patients with MEN 2B often have skeletal abnormalities such as pectus excavatum, talipes equinovarus, pes cavus, slipped femoral epiphysis, aseptic necrosis of lumbar spine, dorsal scoliosis, kyphoscoliosis, lordosis and abnormal dentition (Fig. 2). Almost 100% of patients with MEN 2B have mucosal neuromas (Pujol et al. 1997). Mucosal neuromas are benign tumors of the nerve sheath that may be located anywhere on the mucosal surfaces in the body, but are most common and visible in the anterior portion of the tongue, lips, palate and gums (Fig. 3). They are present at birth or develop early in childhood and are commonly non-pigmented or pale-white, painless papules that measure a few millimeters to one centimeter in size. The presence of these tumors is considered a pathognomonic feature in MEN 2B and any patient found to have one should be screened for MEN 2B by genetic testing (Kebebew and Duh 1998). On light and electron microscopy, the mucosal nodules are plexiform neuromas – that is, uncapsulated masses of convoluted myelinated and unmyelinated nerves surrounded by a tickened

perineurium which elaborate calcitonin (Gorlin et al. 2001). In contrast to neurofibromas histochemical investigation demonstrates absence of both specific and non-specific cholinesterase activity and epithelial membrane antigen negativity.

Cutaneous neuromas are uncommon and when present, are usually located on the face and trunk, appearing as small, well-demarcated papules covered by normal dermis (Truchot et al. 2001). Histologic examination shows an increased number and size of well-circumscribed clusters of small dermal nerves without surrounding inflammation.

Ganglioneuromas throughout the gastrointestinal tract are present in up to 50% of patients with MEN 2B and contribute to dysmotility, abdominal pain, constipation and megacolon. In infancy, gastrointestinal complaints such as constipation or diarrhea may, in fact, be the heralding symptoms of MEN 2B and should be considered in the differential diagnosis.

Medullary thyroid cancer

Medullary thyroid cancer develops within the first decade of life in essentially all patients with MEN 2B and is the leading cause of death. In patients with MEN 2B, medullary thyroid cancer is commonly multicentric, bilateral and lymph node metastasis are commonly present (Kebebew et al. 2000). Medullary thyroid cancer originates from the parafollicular or C-cells (calcitonin secreting) of the thyroid gland. C-cells are concentrated in the posterior and upper one-third of each thyroid lobe. In patients with advanced medullary thyroid cancer, hoarseness and stridor may indicate local invasion, or systemic symptoms from vasoactive hormone secretion may induce flushing and diarrhea, usually in patients with liver metastases (Kebebew et al. 2000).

Pheochromocytoma

Pheochromocytomas, which occur in 20–50% of patients with MEN 2B, are tumors of the adrenal medulla that are derived from the neural crest. They secrete excess catecholamines and usually cause paroxysmal hypertension, headache, palpitations and sweating. They are more likely to be bilateral and extra-adrenal in MEN 2B patients than in patients with sporadic pheochromocytoma. Pheochromocytomas in patients with MEN 2B are usually benign.

In the past, pheochromocytomas accounted for most of the morbidity and mortality in patients with MEN 2B, but this has decreased because of the improved diagnostic accuracy of biochemical testing for elevated catecholamines and metabolites, precise localizing studies, and better perioperative care (Kebebew and Duh 1998).

Natural history

Most patients with MEN 2B come to clinical attention within the first two decades of life. The neurocutaneous manifestation especially oral mucosal neuromas usually develop during the first decade of life. Medullary thyroid cancer and pheochromocytoma usuall present after puberty. Most patients with MEN 2B present with aggressive medullary thyroid cancer, so that most will have persistent or recurrent disease even after complete surgical treatment and are at risk for developing systemic disease. About half of the patients with MEN 2B will develop pheochromocytoma that are commonly bilateral. Most patients with MEN 2B eventually die from metastatic medullary thyroid cancer in the 4th or 5th decade of life.

Pathogenesis and molecular genetics

The RET (*RE*arranged during *T*ransfection) proto-oncogene is responsible for MEN 2 (Lodish and Stratakis 2008). The RET proto-oncogene encodes a transmembrane, tyrosine-kinase receptor-protein that regulates cell growth, migration, and differentiation in neural crest-derived cells located in the thyroid, adrenal medulla, parathyroid glands, enteric and sympathetic nervous system (Pachnis et al. 1993). Activating germline point mutations in the RET proto-oncogene are thought to result in constitutively stimulated tyrosine kinase activity. Point mutations in

the extracellular and intracellular domains have been identified in the MEN 2 syndrome, but all of the mutations documented in MEN 2B patients have been in the intracellular, tyrosine-kinase binding domain (Brandi et al. 2001). Ligands that bind the RET receptor are members of the glial cell-derived neurotrophic factor (GDNF) family (GDNF, persephin, neurturin, artemin) (Baloh et al. 2000). Activation of the RET receptor results in transphosophorylation of numerous tyrosine residues that activate signaling pathways important in cell growth, migration and differentiation. Most cases of MEN 2B occur as a result of germline mutations most commonly in exon 16 (codon 918), and less commonly in exon 14 (codon 883) (Brandi et al. 2001, Machens et al. 2003).

Genotype–phenotype associations have been observed in the MEN 2 syndrome. In MEN 2A, 85% of the RET mutations are present in exon 11 (codon 634) and in MEN 2B, 95% of mutations involve codon 918 (Brandi et al. 2001, Eng et al. 1996, Machens et al. 2003). Because MEN 2B has an autosomal dominant pattern of inheritance, 50% of offspring will be affected with MEN 2B. Of these affected patients, virtually all will develop medullary thyroid cancer and approximately 50% will develop or may already have pheochromocytomas. Almost all patients with MEN 2B have a constellation of distinct phenotypic features. Half of the MEN 2B cases are discovered as hereditary cases; the others present as the index case in which there is a *de novo* RET germline mutation and no other affected family members (Norum et al. 1990).

Diagnosis, follow-up and management

The presence of mucosal neuromas are enough to diagnose most patients with MEN 2B and occur within the first decade of life. Mucosal neuromas are extremely rare, perhaps unheard of, outside of the MEN 2B syndrome. Other phenotypic features such as a tall, lanky, marfanoid body habitus, and a narrow face are also commonly present but not specific to MEN 2B. If diagnosed clinically all patients will have medullary thyroid cancer with or without pheochromocytoma in association with the phenotypic features of MEN 2B. Today, with the implementation of genetic screening for RET germline mutations, some patients may have none of the obvious phenotypic features, no medullary thyroid cancer, and pheochromocytoma if diagnosed at infancy or at a very young age.

Medullary thyroid cancer

Fine needle aspiration biopsy and cytologic examination of neck masses are accurate for diagnosing medullary thyroid cancer, especially when used with immunohistochemical staining for the presence of amyloid, calcitonin, and carcinoembryonic antigen.

Surgical treatment consisting of total thyroidectomy and removal of cervical lymph nodes and is the only effective treatment for medullary thyroid cancer. Unlike follicular cells of the thyroid gland, the C-cells do not trap iodine so radioiodine ablation is not effective. Chemotherapy and external-beam radiation therapy are generally ineffective. Basal and stimulated serum calcitonin measurement is indispensable as a tumor marker to detect persistent or recurrent medullary thyroid cancer after surgical resection. The mortality due to medullary thyroid cancer in patients with MEN 2B patients is 20–33% at 10 years follow up (Brauckhoff et al. 2004, O'Riordain et al. 1995).

Pheochromocytoma

The diagnosis of pheochromocytoma is established by measuring 24-hour urinary levels of catecholamine and metabolites. All patients diagnosed with medullary thyroid cancer should have biochemical testing to exclude a diagnosis of pheochromocytoma before thyroidectomy because an undiagnosed pheochromocytoma may result in hypertensive crisis and death during the operation (Sutton et al. 1981). Imaging studies including CT scans, MRI and MIBG scans are used to localize the tumor and rule out bilateral or extra-adrenal disease, which are frequently found in patients with MEN 2B (Kebebew and Duh 1998). Laparoscopic adrenalectomy, preceded by meticulous preoperative preparation with alpha and beta-blockade is the optimal treatment approach and reduces perioperative morbidity and mortality (Lairmore et al. 1993).

Differential diagnosis

Because of the distinct physical features of patient with MEN 2B they can easily be distinguished from the other types of MEN 2 syndrome. In young patients who may not have the characteristic features of MEN 2B, testing for germline RET mutation in codons 833 and 918 are specific for MEN 2B.

Genetic counseling

Because MEN 2B is an autosomal dominant hereditary syndrome with an early and 100% penetrance, affected individuals and at risk family should have early genetic counseling. Fortunately, the responsible gene for the MEN 2 syndrome is known and performing direct DNA sequencing for RET mutations is accurate.

Genetic counseling should focus in patient education, comprehensive family history collection and review of medical records. Genetic screening is more accurate than basal or stimulated calcitonin measurement for screening patients at risk for MEN 2. In a family with a known RET germline mutation, MEN 2 can be safely ruled out if no RET mutation is identified in that individual. At least two separate blood samples should show the same RET germline mutation before a patient is determined to be a gene carrier. RET germline mutations in codons 918 and 883 have the earliest age for presenting with medullary thyroid cancer, as early as 9 months of age (Machens et al. 2003). Because MEN 2B cases have germline RET mutations in codons 918 and 883, family members should be screened at birth or before the age of 1 year. All patients found to be gene carriers should have prophylactic thyroidectomy with central neck node dissection as soon as the diagnosis is made and screening for pheochromocytoma (Gertner and Kebebew 2004).

Summary

Although MEN 2B is an uncommon hereditary syndrome, most patients develop aggressive medullary thyroid cancer and pheochromocytomas. The physical and neurocutaneous features of MEN 2B patients are specific, and should increase the index of suspicion because half of the MEN 2B cases present as the index case and can be recognized early in childhood if one is aware of these features. Early genetic screening and diagnosis affords patients with MEN 2B the only chance at curative treatment for medullary thyroid cancer and pheochromocytoma, and permits other family members to be screened. Family members of a patient with a known RET mutation who are found to be negative for the RET proto-oncogene mutation can be assured that they are not at risk for developing MEN 2 and require no further follow-up.

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