Syndrome of the month

Multiple endocrine neoplasia type 2B (mucosal neuroma syndrome, Wagenmann-Froboese syndrome)

P J Morrison, N C Nevin

Abstract

Multiple endocrine neoplasia type 2B (MEN 2B), or the mucosal neuroma syndrome, is an autosomal dominant hamartoneoplastic syndrome. Features include multiple mucosal neuromas, phaeochromocytoma, medullary thyroid carcinoma, and Marfanoid body habitus with a characteristic dysmorphic facies. The gene responsible is the receptor tyrosine kinase (RET) proto-oncogene on chromosome 10. The mutational spectrum of MEN 2B is remarkably narrow, with over 95% of cases being caused by a single methionine to threonine substitution in the intracellular tyrosine kinase domain. Recent biochemical evidence suggests that this mutation alters the substrate specificity of intracellular signal transduction.

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Key words: multiple endocrine neoplasia type 2B; mucosal neuroma syndrome; Wagenmann-Froboese syndrome.

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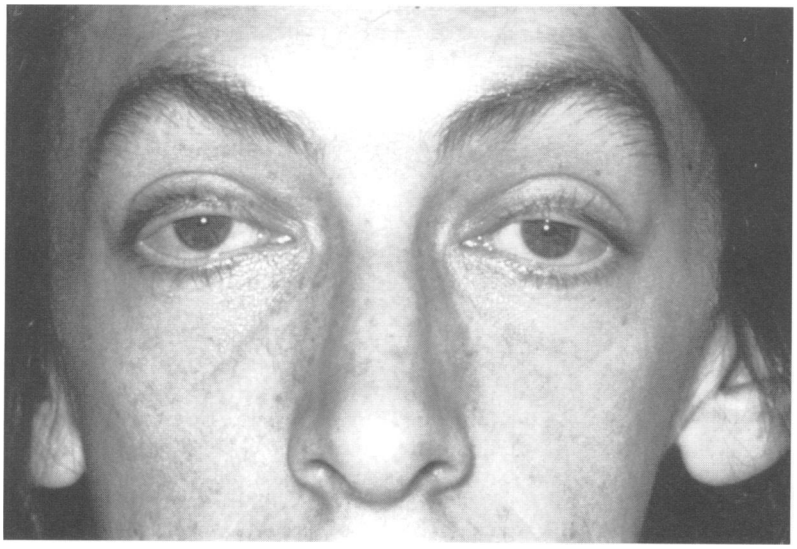

Figure 1 The upper face in MEN 2B showing thickening and eversion of the upper eyelid margins and prominent eyebrows.

Multiple endocrine neoplasia type 2B (MEN 2B) was described initially by Wagenmann[1] and Froboese.[2] Others, including Williams and Pollock[3] and Gorlin and Vickers,[4] have delineated the expanded phenotype. As in other hamartoneoplastic syndromes, autosomal dominant inheritance has been shown. MEN 2B, along with MEN 2A and familial medullary thyroid carcinoma (FMTC), are caused by mutations in the RET proto-oncogene on chromosome 10. MEN 2B differs from MEN 2A and FMTC, however, in that it is characterised by additional neuroendocrine abnormalities. The features of the three conditions are shown in table 1.

Clinical features

MEN 2B has a characteristic phenotype with medullary thyroid carcinoma (MTC) and phaeochromocytoma. The face may give a wide eyed expression with thickening and eversion of the upper eyelid margins and visible tarsal plates (fig 1). Neuromas may be present on the eyelids and conjunctiva, and prominent thickened corneal nerves that extend to the pupillary area may be seen on slit lamp examination.[5] The eyebrows are large and prominent (fig 1).

The face is elongated with prominent "blubbery" lips and submucosal nodules present on the vermilion border, often laterally (fig 2). Oral manifestations, which are often the first clue to the syndrome in infancy or early childhood, include mucosal neuromas on the anterior dorsal surface of the tongue (fig 3). Mucosal neuromas of the tongue are almost pathognomonic in the presence of medullary thyroid carcinoma. Other oral features include palatal and pharyngeal neuromas, a high arched palate, and a prominent jaw.

Virtually all patients have medullary thyroid carcinoma which appears to be more aggressive than in MEN 2A, with average age at death around 21 years.[6] Because of this reduced survival, around 50% of cases of MEN 2B are sporadic. Phaeochromocytoma are present in 50% of cases, of which half are multiple and often bilateral. This percentage increases with age, and is lower than in MEN 2A again because of the shorter life span. A small

Table 1 Organ systems invoved in the MEN 2 syndromes

Disease	*Thyroid (%)*	*Adrenal (%)*	*Parathyroid (%)*	*Enteric ganglia (%)*	*Mucosa (%)*	*Skeletal (%)*
MEN 2A	100	50-70	25	Rare	—	—
FMTC	100	—	—	—	—	—
MEN 2B	100	50	—	> 40	100	75
HSCR	—	—	—	100	—	—

proportion of patients with undiagnosed phaeochromocytoma may die from a cardiovascular crisis perioperatively.[6 7]

There is a Marfanoid habitus in 75% of patients,[8] often with proximal muscle wasting and weakness. Other musculoskeletal manifestations include kyphoscoliosis or lordosis, joint laxity, decreased subcutaneous fat, pes cavus, and slipped capital femoral epiphysis.[6] Gastrointestinal problems include abdominal distension, megacolon, constipation, or diarrhoea resulting from diffuse ganglioneuromatosis. C cell hyperplasia of the thyroid cells causes calcitonin secretion and abnormal regulation of hormones allows release of histamine, serotonin, and prostaglandins among others.[4]

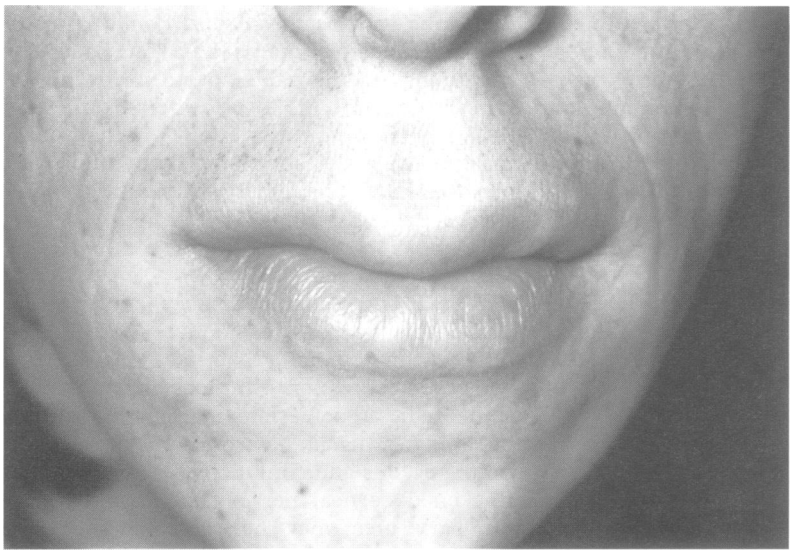

Figure 2 Subcutaneous thickening of the perioral region, with prominent "blubbery" lips and a submucosal nodule visible on the upper left lateral vermilion border.

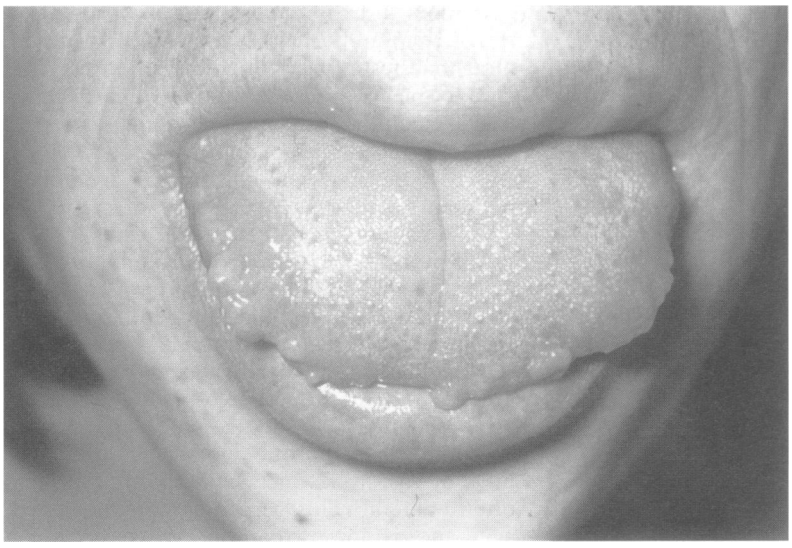

Figure 3 Multiple mucosal neuromas on the anterior dorsal surface of the tongue.

Differential diagnosis

Medullary thyroid carcinoma is seen in MEN type 2A (MTC, phaeochromocytoma or parathyroid adenoma or both, but without other neuroendocrine or dysmorphic features) and also familial medullary thyroid carcinoma (or FMTC, more than four patients within a family with MTC and no evidence of phaeochromocytoma on active screening). Familial autosomal dominant phaeochromocytoma may occur in isolation, or as part of other tumour syndromes including Von-Hippel Lindau disease and neurofibromatosis I and II. Familial intestinal pseudo-obstruction may occur as an autosomal dominant trait.[9] Raised calcitonin levels, especially if stimulated by intravenous pentagastrin injection, are very suggestive of medullary thyroid carcinoma. CT of the adrenal glands may show the presence of phaeochromocytoma. Intestinal ganglioneuromatosis has a characteristic appearance on barium enema with alternating areas of dilatation and narrowing.[10]

Aetiology and genetics

MEN 2B is inherited as an autosomal dominant trait. Linkage to chromosome 10 was described in 1990.[11] In 1993, mutations in the proto-oncogene RET (REarranged during Transfection) were described in MEN 2A and FMTC, and it was suggested that MEN 2B could also be caused by a mutation within the RET oncogene.[12 13] This was confirmed in 1994.[14-16] Over 95% of MEN 2B patients have a specific point mutation at codon 918 in exon 16 of RET resulting in the replacement of methionine by threonine. One MEN 2B family has been shown not to have this mutation, although no mutation in this family has yet been identified.[17] Another family has been shown to have an additional sequence variant resulting in a substitution of a tyrosine for a serine at position 922.[18] The methionine at codon 918 is preserved in mouse proto-RET,[19] and also in other receptor type tyrosine kinases,[20] suggesting that this may be a crucial functional mutation.

Mutations in the RET gene cause four conditions, MEN 2A, FMTC, MEN 2B, and Hirschsprung disease (HSCR). HSCR is not a cancer syndrome, with only some cases caused by RET mutations.[21] It is worth noting that overgrowth rather than absence of enteric ganglia is a prominent feature of MEN 2B. All four conditions involve expression of RET in embryonic thyroid C cells, adrenal medulla, parathyroid, and autonomic nerve plexi of the gut,[22] which are all developmentally related. Most features of MEN 2B can thus be easily explained, but some of the skeletal features are not so easily explained by this model.

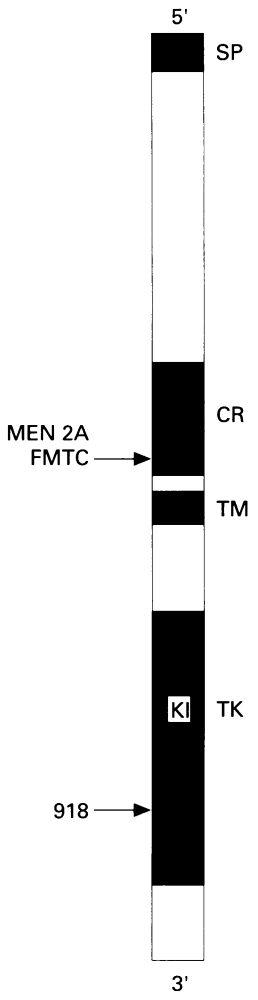

Figure 4 Diagram of the RET proto-oncogene showing the location of the majority of MEN 2A and FMTC mutations (arrow), and the site of the 918 MEN 2B mutation (arrow). Shaded areas represent the following: SP = signal peptide, CR = cysteine residues, TM = transmembrane domain, TK = tyrosine kinase domain, KI = kinase insert within the TK domain.

The structure of the RET gene is shown in fig 4. The RET proto-oncogene contains 28 cysteine residues, and encodes a transmembrane receptor tyrosine kinase. Mutations associated with MEN 2A and FMTC involve cysteine residues in the extracellular domain of this receptor (fig 4). MEN 2B is associated with the 918 mutation in the intracellular tyrosine kinase (TK) domain. There is some correlation between MEN 2A mutations and phenotype; mutations at codon 634 are more often associated with MEN 2A than FMTC and there is a predisposition to phaeochromocytoma and parathyroid disease at this site.

MEN 2B is a much more aggressive condition than MEN 2A or FMTC. RET MEN 2B mutations alter the substrate specificity of RET,[23 24] which may result in alteration of RET activity at a post receptor level giving organ specific growth advantage. HSCR is associated with a variety of mutations scattered along the whole gene. RET mutations in HSCR appear to be recessive at the cellular level and RET appears to play a role in the development of the enteric nervous system.[25]

MEN 2A, like MEN 2B, has a gain of function, although MEN 2A acts by converting RET into a transforming gene through ligand independent dimerisation,[23] rather than a change in substrate specificity. In normal RET, ligand binding is followed by receptor dimerisation and activation of the TK domain. The RET ligand has not yet been identified but the MEN 2B mutation allows altered substrate phosphorylation independent of dimerisation.[25] The catalytic specificity of protein kinases is critical for selective downstream signalling in cells. Receptor tyrosine kinases preferentially phosphorylate peptides recognised by their own group III Src-homology-2 (SH2) domains.[24] These domains recognise phosphotyrosine in a specific sequence context. The 918 mutation in MEN 2B is in a region of domain VIII that is responsible for peptide substrate selectivity; this mutation affects enzymatic activity and its interaction with different substrates. The wild type RET protein has a methionine at residue 918; mutation to a threonine causes preferential phosphorylation similar to SH2 containing protein tyrosine kinases.[24] Other studies using biochemical analysis of the RET MEN 2B protein show a greater increase in autophosphorylation and TK activity than in the wild type,[25] supporting a gain of function for this mutation.

The MEN 2B mutation differs in function from MEN 2A mutations. Transfection of RET in NIH 3T3 cell fibroblasts shows qualitatively and quantitatively altered RET catalytic properties in MEN 2B,[23] with MEN 2A showing less autophosphorylation. This confirms differential phosphorylation in the MEN 2B transfectants and establishes that mutations in MEN 2A and MEN 2B convert RET into a dominant transforming gene through oncogenic conversion rather than a loss of suppressor function. This shows that germline transmission of a dominant transforming gene can occur in a human cancer. The more extensive MEN 2B phenotype could be explained by tissue specific differences in substrates, each with a unique mitogenic potential.[25]

Although MEN 2A shows allelic heterogeneity, this is not seen in MEN 2B because of the common 918 mutation. MEN 2B cases are de novo in 50%, and parental origin is almost exclusively paternal.[26] This is not unique in tumour syndromes; several, including Wilms tumour, bilateral retinoblastoma, osteosarcoma, and neurofibromatosis I, show a paternal origin predominance.[27] Some syndromes, such as Cowden syndrome,[28] appear to show more severe expression through maternal transmission.

Another unusual feature for an "autosomal dominant" disease is that no distortion of the sex ratio in offspring is seen with paternally inherited MEN 2B, but maternally inherited alleles result in twice as many affected males as females.[26] This is the opposite to that found in bilateral retinoblastoma cases. Explanations for this observation could include an additional disease associated gene or an embryonic lethal effect.[29] Not enough pieces of the jigsaw are as yet available to see the whole solution clearly.

Management

All people at risk or suspected of having MEN 2B should have mutational analysis for the RET gene as early as possible. In most cases this will provide presymptomatic diagnosis, or confirm the diagnosis. Prophylactic total thyroidectomy[30] is advocated for people who are shown to inherit the mutation. The ideal age for surgery is preferably before the age of 4 years,[31] as medullary thyroid carcinomas in MEN 2B are particularly aggressive and metastatic spread may occur before the age of 10. Continued follow up of all affected or gene "positive" subjects should include annual screening for both medullary cancer by basal or stimulated calcitonin, and for phaeochromocytoma by standard urine and imaging techniques.[30] The identification of the underlying molecular and biochemical mechanisms of RET activation above will be used in future therapeutic strategies.

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