Syndrome of the month

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Mucosal neuromata syndrome (MEN type IIb (III))

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According to the classification of Steiner *et al*¹ three syndromes characterised by multiple neoplasms of the endocrine glands have been delineated: multiple endocrine neoplasia (MEN) type I (McKusick No *13110), MEN type IIa or II (*17140), and MEN type IIb or III (*16230). The type and incidence of the major lesions in the three MEN syndromes² are summarised in the table. The clinical entity in which multiple mucosal neuromas, phaeochromocytoma, and medullary thyroid carcinoma are combined (MEN IIb or III) was first described by Williams and Pollock³ and has been further detailed by Schimke *et al*⁴ and Gorlin *et al*.^{5,6}

Clinical course

An intriguing observation in MEN type IIb (III) is the association of multiple endocrine neoplasia with a distinct phenotype, mucosal neuromas, intestinal ganglioneuromatosis, and neurological findings.

THE DISTINCT PHENOTYPE (FIGS 1 TO 3)

A slim, asthenic, Marfanoid habitus is present in all patients and there is also a variable degree of muscle wasting. In some patients, the muscle wasting may be severe, simulating a myopathic state.^{4,7-12} This muscle wasting is apparently responsible for the appearance of different skeletal deformities, such as kyphoscoliosis, pes cavus, genu valgum, and increased joint mobility.^{4,6,13} The face is elongated with large, 'blubbery', nodular lips (also called bumpy, patulous lips).^{4-6,12,14-16} Neuromas may involve the eyelids, conjunctivae, and corneae and this results in thickening and eversion of the eyelids and linear, yellowish elevations and infiltrations of the conjunctivae. Enlarged corneal nerves are observed on slit lamp examination.¹⁷ Examination of the skin may reveal café au lait spots, cutaneous neuromas, circumoral or midfacial lentiginosis,^{7,18,19}

and diffuse pigmentation of the hands and feet.^{20,21} Baum²² described an abnormal histamine skin test (absent axon flare response) in a patient with MEN type IIb (III) and this was confirmed by Carney *et al*²³ in 13 other patients: after histamine injection a weal developed at the injection site in all patients with MEN type IIb (III). Pubertal delay was noted in several patients.^{4,8,12}

MUCOSAL NEUROMAS

MEN type IIb (III) is characterised by the appearance of multiple plexiform neuromas and thickening of the nerves. They may be present from birth and may be localised in the submucosa of virtually all organs and also on the spinal nerve roots.⁴ This results in the involvement of lips, tongue, and eyes with generalised or localised thickening of these organs with the characteristic clinical changes. Submucosal neuromas can also be found in the

TABLE Types and incidence of the major lesions in the MEN syndromes.

Syndrome	Lesions	Incidence (%)
MEN I (Werner's syndrome)	Parathyroid adenomas and/or hyperplasia	90
	Pancreatic islet tumours	80
	Pituitary tumours	65
	Adrenal cortical adenomas	38
	Thyroid adenomas	19
MEN II or (IIa) (Sipple's syndrome)	Medullary thyroid carcinoma	100
	Phaeochromocytoma	>50
	Parathyroid adenomas and/or hyperplasia	25-50
MEN III (or IIb) (Froboese's syndrome, mucosal neuromata syndrome)	Medullary thyroid carcinoma	100
	Phaeochromocytoma	50
	Parathyroid adenoma or hyperplasia	0
	Mucosal neuromas	100
	Intestinal ganglioneuromatosis	100

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gingiva, palate, nose, pharynx, larynx, bronchi, and bladder.^{4 24} Hyperplasia of the neurenteric ganglion cells is found throughout the entire gastrointestinal tract wall. On the basis of light and electron microscopic histology, Miller *et al*²⁵ postulated that these tumours represent hypertrophy of axons similar to that noted in amputation neuromas.

GASTROINTESTINAL SYSTEM

In addition to the appearance of a diffuse gastrointestinal ganglioneuromatosis which may result in

FIG 2 Multiple neuromas on the tongue.

FIG 3 Infiltration of the eyelids with ectropion and linear infiltration of the conjunctiva.

diverticulosis, persistent diarrhoea or, less frequently, constipation with megacolon, may be an early, important symptom in patients with MEN type IIb (III).^{3 10 13 26 27} The bowel malfunction may be explained by the bizarre hyperplasia of the ganglion cells and, in addition, the diarrhoea may result from elaboration of prostaglandins by medullary carcinoma of the thyroid.²⁸ X ray examination of the lower gastrointestinal tract may show abnormal haustral markings, thickened mucosal folds, diverticula, and dilatation; these findings have been misdiagnosed as ulcerative colitis, Crohn's disease, or congenital megacolon.^{13 29} These gastrointestinal symptoms were the first complaint of the patient illustrated in this paper.

NEUROLOGICAL FINDINGS

Dyck *et al*¹¹ reported distinct clinical and electrophysiological abnormalities in the neurological examinations of patients with MEN type IIb (III). Five of their six patients had mild to moderate weakness of the ankle dorsiflexor muscles and of the intrinsic foot muscles. Chronic neurogenic atrophy was found by needle electromyographic examination of limb muscles in three of the six patients. They provided strong evidence that the somatic nervous system, as well as the autonomic, is involved in MEN type IIb (III).

Endocrine neoplasia

As indicated in the table the appearance of endocrine tumours (medullary carcinoma of the thyroid and pheochromocytoma) is the most life threatening symptom in MEN type IIb (III). The medullary

carcinoma of the thyroid is of multifocal origin and arises from parafollicular or 'C cells' which are derived from the neural crest.^{9 30-33} The risk of developing this tumour in patients with MEN type IIB (III) is almost 100%.² It is more aggressive and occurs earlier than in MEN type IIA.^{10 34 35} In comparison to sporadic medullary thyroid carcinoma (53 years), the mean age of diagnosis of this tumour in MEN type IIB (III) is 19.6 years.³⁶ The tumour secretes different active substances such as an ACTH-like substance, serotonin, and other monoamines, DOPA decarboxylase, prostaglandin, histaminase, and calcitonin.^{28 37-41} These are responsible for a variety of clinical symptoms of which diarrhoea, Cushing's syndrome, and abnormal histamine reaction are the most important. Carcinoembryonic antigen secreted by the tumour cells is, together with calcitonin, an important diagnostic and prognostic tumour marker in this condition.⁴² Presymptomatic thyroidectomy is recommended in all patients and family screening must be based on careful clinical and biochemical screening and follow up.^{12 13 34 35 43-46}

In MEN type IIB (III) pheochromocytoma is, like the medullary thyroid carcinoma, of multiple origin and derived from neural crest cells. The frequency of pheochromocytoma increases considerably with age, particularly after the age of 20 years (23% under 20 years to 90% in the older group).¹³

Incidence

No reliable figures are available on the incidence of this syndrome. So far, fewer than 150 patients with this condition have been reported and it appears to be less frequent than MEN type I and MEN type IIA.¹³

Inheritance

As with MEN type I and type IIA, MEN type IIB (III) is inherited as an autosomal dominant trait with variable expression. Male to male transmission was reported by Barlett *et al.*⁴⁷ Both sexes are equally affected and about half of the cases appear to be sporadic, even after careful family examination.¹³ There is no evidence so far as to whether the gene is located on chromosome 10, as recently shown for MEN type IIA.

Pathogenesis

This syndrome most probably results from a dysplasia of neuroectodermal tissue. All the components of MEN type IIB (III) can be attributed to hyperplasia or neoplasia of neural crest cells: parafollicular cells of the thyroid (origin of the medullary thyroid carcinoma) and the medullary portion of the adrenal gland (origin of pheochromocytoma), mucosal neuromas, medullated corneal nerve fibres, and ganglioneuromatosis of the gastrointestinal tract.^{2 4 6 13 24 33 48 49} There is no agreement about whether the tumour genesis is controlled by a single or a two step mutation mechanism.^{2 13 50 51}

References

- Steiner AL, Goodman AD, Powers SR. Study of kindred with pheochromocytoma, medullary thyroid carcinoma, hyperparathyroidism and Cushing's disease: multiple endocrine neoplasia, type 2. *Medicine (Baltimore)* 1968;47:371-409.
- Baylin SB. The multiple endocrine neoplasia syndromes: implications for the study of inherited tumors. *Semin Oncol* 1978;5:35-45.
- Williams ED, Pollock DJ. Multiple mucosal neuromata with endocrine tumors: a syndrome allied to Von Recklinghausen's disease. *J Pathol Bacteriol* 1966;91:71-80.
- Schimke RN, Hartmann WH, Prout TE, Rimoin DL. Syndrome of bilateral pheochromocytoma, medullary thyroid carcinoma and multiple neuromas. A possible regulatory defect in the differentiation of chromaffin tissues. *N Engl J Med* 1968;279:1-7.
- Gorlin RJ, Sedano HO, Vickers RA, Cervenka J. Multiple mucosal neuroma, pheochromocytoma and medullary carcinoma of the thyroid: a syndrome. *Cancer* 1968;22:293-9.
- Gorlin RJ, Mirkin BL. Multiple mucosal neuromas, pheochromocytoma, medullary carcinoma of the thyroid and Marfanoid body build with muscle wasting. *Z Kinderheilkd* 1972;113:313-25.
- Cunliffe WJ, Hudgson P, Fulthorpe JJ, *et al.* A calcitonin-secreting medullary thyroid carcinoma associated with mucosal neuromas, marfanoid features, myopathy and pigmentation. *Am J Med* 1970;48:120-6.
- Levy M, Habib R, Lyon G, Schweiguth O, Lemerle J, Roger P. Neuromatose et epithelioma a stroma amyloide de la thyroide chez l'enfant. *Arch Fr Pediatr* 1970;27:561-83.
- Gorlin RJ, Vickers RA. Multiple mucosal neuromas, pheochromocytoma, medullary carcinoma of the thyroid and Marfanoid body build with muscle wasting: reexamination of a syndrome of neural crest malmigration. *Birth Defects* 1971;VII(6):69-72.
- Moyes CD, Alexander FW. Mucosal neuroma syndrome presenting in a neonate. *Dev Med Child Neurol* 1977;19:518-21.
- Dyck PJ, Carney JA, Sizemore GW, Okazaki H, Brimijoin WS, Lambert EH. Multiple endocrine neoplasia, type 2b: phenotype recognition, neurological features and their pathological basis. *Ann Neurol* 1979;6:302-14.
- White MP, Goel KM, Connor JM, Coutts NA. Mucosal neuroma syndrome—a phenotype for malignancy. *Arch Dis Child* 1985;60:876-7.
- Khairi MRA, Dexter RN, Burzynski NJ, Johnston CC. Mucosal neuroma, pheochromocytoma, and medullary thyroid carcinoma: multiple endocrine neoplasia type 3. *Medicine (Baltimore)* 1975;54:85-112.
- Forsman PJ, Jenkins ME. Medullary carcinoma of the thyroid with Marfan-like body habitus. *Pediatrics* 1973;52:188-91.
- Casino AJ, Sciubba JJ, Ohri GL, *et al.* Oral-facial manifestations of the multiple endocrine neoplasia syndrome. *Oral Surg* 1981;51:516-23.
- Raue F, Komposch G, Ziegler R. Schleimhautneurome an Lippen und Zunge. Leitsymptome bei der multiplen endokrinen Neoplasie Type IIB. *Dtsch Zahnärztl Z* 1986;41:1000-1.
- Spector B, Klintworth GK, Wells SA. Histologic study of the ocular lesions in multiple endocrine neoplasia syndrome type IIB. *Am J Ophthalmol* 1981;91:204-15.

- ¹⁸ Bazex A, Dupré A. Neuromes myeliniques muqueux à localisation centrofaciale et laryngée. Neuromes des lèvres, de la langue des paupières, des narines, du larynx (entité nouvelle?). *Ann Dermatol Venerol* 1958;**85**:613-41.
- ¹⁹ Calmettes L, Bazex A, Deodati F, Dupré A, Bec P. Manifestations oculo-palpébrales des neuromes myéliniques muqueux. *Arch Ophthalmol* 1959;**19**:257-69.
- ²⁰ Thies W. Multiple echte fibrilläre Neurome (Rankenneurome) der Haut und Schleimhaut. *Arch Klin Exp Dermatol* 1964;**218**:561-73.
- ²¹ Ljungberg O, Cederquist E, Von Studnitz W. Medullary thyroid carcinoma and pheochromocytoma—a familial chromatoffinosis. *Br Med J* 1967;**i**:279-81.
- ²² Baum JL. Abnormal intradermal histamine reaction in the syndrome of pheochromocytoma, medullary carcinoma of the thyroid gland and multiple mucosal neuromas. *N Engl J Med* 1971;**284**:963-4.
- ²³ Carney JA, Hayles AB, Pearce AGE, Perry HO, Sizemore GW. Abnormal cutaneous innervation in multiple endocrine neoplasia, type 2b. *Ann Intern Med* 1981;**94**:362-3.
- ²⁴ Ruppert RD, Buerger LF, Chang WWL. Pheochromocytoma, neurofibromatosis and thyroid carcinoma. *Metabolism* 1966;**15**:537-41.
- ²⁵ Miller RL, Burzynski NJ, Giammana BL. The ultrastructure of oral neuromas in multiple mucosal neuromas, pheochromocytoma, medullary thyroid carcinoma syndrome. *J Oral Pathol* 1977;**6**:253-63.
- ²⁶ Carney JA, Go VLW, Sizemore GW, Hayles AB. Alimentary tract ganglioneuromatosis: a major component of the syndrome of multiple endocrine neoplasia, type 2b. *N Engl J Med* 1976;**295**:1287-91.
- ²⁷ Whittle TS, Goodwin MN. Intestinal ganglioneuromatosis with the mucosal neuromamedullary thyroid carcinoma-pheochromocytoma syndrome. *Am J Gastroenterol* 1976;**65**:249-57.
- ²⁸ Williams ED, Karim SMM, Sandler M. Prostaglandin secretion by medullary carcinoma of the thyroid—a possible cause of associated diarrhoea. *Lancet* 1968;**i**:22-3.
- ²⁹ Anderson TE, Speckman TJ, Schwartz SS. Roentgen findings in intestinal ganglioneuromatosis. Its association with medullary thyroid carcinoma and pheochromocytoma. *Radiology* 1971;**101**:93-6.
- ³⁰ Hazard JB, Hawk WA, Crile G. Medullary (solid) carcinoma of the thyroid-clinicopathologic entity. *J Clin Endocrinol* 1959;**19**:152-61.
- ³¹ Dube WJ, Bell GO, Aliopoulos MA. Thyreocalcitonin activity in metastatic medullary thyroid carcinoma. Further evidence for its parafollicular cell origin. *Arch Intern Med* 1969;**123**:423-7.
- ³² Le Dourain N. Sur l'origine des cellules à calcitonine du corps ultimobranchial de l'embryon d'oiseau. *C R Assoc Anat* 1971;**152**:558-68.
- ³³ Pearce AGE, Polak JM. Cytochemical evidence for the neural crest origin of mammalian ultimobranchial C cells. *Histochemistry* 1971;**27**:96-102.
- ³⁴ Norton JA, Froome LC, Farrell RE, Wells SA. Multiple endocrine neoplasia type IIb. The most aggressive form of medullary thyroid carcinoma. *Surg Clin North Am* 1979;**59**:109-18.
- ³⁵ Kaufman FR, Roe TF, Isaacs H Jr, Weitzman JJ. Metastatic medullary thyroid carcinoma in young children with mucosal neuroma syndrome. *Pediatrics* 1982;**70**:263-7.
- ³⁶ Ibanez ML, Cole VW, Russel WO, Clark RL. Solid carcinoma of the thyroid gland—analysis of 53 cases. *Cancer* 1967;**20**:706-23.
- ³⁷ Falck B, Ljungberg O, Rosengren E. On the occurrence of monoamines and related substances in familial medullary thyroid carcinoma with pheochromocytoma. *Acta Pathol Microbiol Scand* 1968;**74**:1-10.
- ³⁸ Baylin SB, Beaven MA, Keiser HR, Tashjian AH Jr, Melvin KEW. Serum histaminase and calcitonin levels in medullary carcinoma of the thyroid. *Lancet* 1972;**i**:455-8.
- ³⁹ Atkins FL, Beaven MA, Keiser HR. DOPA decarboxylase in medullary carcinoma of the thyroid. *N Engl J Med* 1973;**289**:545-8.
- ⁴⁰ Voelkel EF, Tashjian AH Jr, Davidoff FF, Cohen RB, Perlia CP, Wurtman RJ. Concentrations of calcitonin and catecholamines in pheochromocytomas, a mucosal neuroma and medullary thyroid carcinoma. *J Clin Endocrinol Metab* 1973;**37**:297-307.
- ⁴¹ Birkenhäger JC, Upton GV, Seldenrath HJ, Krieger DT, Tashjian AH Jr. Medullary thyroid carcinoma: ectopic production of peptides with ACTH-like, corticotropin releasing factor-like and prolactin producing-stimulating activities. *Acta Endocrinol (Copenh)* 1976;**83**:280-92.
- ⁴² DeLellis RA, Rule AH, Spiler I, Nathanson L, Tashjian AH Jr, Wolfe HY. Calcitonin and carcinoembryonic antigen as tumor markers in medullary thyroid carcinoma. *Am J Clin Pathol* 1978;**70**:587-94.
- ⁴³ Melvin KEW, Miller HH, Tashjian AH. Early diagnosis of medullary carcinoma of the thyroid gland by means of calcitonin assay. *N Engl J Med* 1971;**285**:1115-20.
- ⁴⁴ Baylin SB. Medullary carcinoma of the thyroid gland: use of biochemical parameters in detection and surgical management of the tumor. *Surg Clin North Am* 1974;**54**:309-23.
- ⁴⁵ Block MA, Jackson CE, Tashjian AH Jr. Management of occult medullary thyroid carcinoma, evidenced only by serum calcitonin level elevations after apparently adequate neck operations. *Arch Surg* 1978;**113**:368-72.
- ⁴⁶ Imai Y, Fukase M, Tsutsumi M, et al. A case of multiple endocrine neoplasia type IIb: endocrinological evaluation and family screening. *Endocrinol Jpn* 1982;**29**:49-56.
- ⁴⁷ Barlett RC, Myall RWT, Bean LR, Mandelstam P. A neuroendocrine syndrome: mucosal neuromas, pheochromocytoma and medullary carcinoma. *Oral Surg* 1971;**31**:206-20.
- ⁴⁸ Pearce AGE, Polak JM. Neural crest origin of the endocrine polypeptide (APUD) cells of the gastrointestinal tract and pancreas. *Gut* 1971;**12**:783-8.
- ⁴⁹ Pearce AGE. The APUD cell concept and its implications in pathology. *Pathol Annu* 1974;**9**:27-41.
- ⁵⁰ Knudson AG Jr, Strong LC. Mutation and cancer: neuroblastoma and pheochromocytoma. *Am J Hum Genet* 1972;**24**:514-32.
- ⁵¹ Cerny JC, Jackson ChE, Talpos GB, Yott JB, Lee MW. Pheochromocytoma in multiple endocrine neoplasia type II. An example of the two-hit theory of neoplasia. *Surgery* 1982;**92**:849-52.

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