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 ¹⁴-¹⁵ Neuromas may involve the eyelids, conjunctivae, and cornea and this results in thickening and erosion 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, circumanal or midfacial lentigiosis,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>
<thead>
<tr>
<th>Syndrome</th>
<th>Lesions</th>
<th>Incidence (%)</th>
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<tbody>
<tr>
<td>MEN I (Werner’s syndrome)</td>
<td>Parathyroid adenomas and/or hyperplasia</td>
<td>90</td>
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<tr>
<td></td>
<td>Pancreatic islet tumours</td>
<td>80</td>
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<tr>
<td></td>
<td>Pituitary tumours</td>
<td>65</td>
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<tr>
<td></td>
<td>Adrenal cortical adenomas</td>
<td>38</td>
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<tr>
<td></td>
<td>Thyroid adenomas</td>
<td>19</td>
</tr>
<tr>
<td>MEN II or (IIa) (Sipple’s syndrome)</td>
<td>Medullary thyroid carcinoma</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Phaeochromocytoma</td>
<td>&gt;50</td>
</tr>
<tr>
<td></td>
<td>Parathyroid adenomas and/or hyperplasia</td>
<td>25-50</td>
</tr>
<tr>
<td>MEN III (or IIb) (Frobose’s syndrome, mucosal neuromata syndrome)</td>
<td>Medullary thyroid carcinoma</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Phaeochromocytoma</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Parathyroid adenoma or hyperplasia</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mucosal neuromas</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Intestinal ganglioneuromatosis</td>
<td>100</td>
</tr>
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gingiva, palate, nose, pharynx, larynx, bronchi, and bladder.\(^\text{24}\) 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.\(^\text{25}\) 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 diverticulosis, persistent diarrhoea or, less frequently, constipation with megacolon, may be an early, important symptom in patients with MEN type IIb (III).\(^\text{3,10,13,26,27}\) 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.\(^\text{28}\) 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.\(^\text{13,29}\) These gastrointestinal symptoms were the first complaint of the patient illustrated in this paper.

**NEUROLOGICAL FINDINGS**

Dyck et al.\(^\text{11}\) 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 phaeochromocytoma) is the most life threatening symptom in MEN type IIb (III). The medullary
Mucosal neuromata syndrome (MEN type IIb (III))

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 phaeochromocytoma), 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 30 51

References

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