Medullary Carcinoma of the Thyroid in the Multiple Mucosal Neuromas Syndrome*

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ABSTRACT

The clinical features of the multiple mucosal neuromas (MMN) syndrome permit the recognition of these patients and their potential development of the associated medullary thyroid carcinoma (MTC). The distinctive physical appearance caused by the mucosal neuromas, the Marfanoid habitus and, occasionally, the positive family history aid in establishing the diagnosis. Neurogangliomas are frequently present in the gastrointestinal tract of these patients who may have megacolon, constipation and diarrhea. The third instance of the MMN syndrome is reported in the newborn as intestinal obstruction. It is suggested that the syndrome be considered in the differential diagnosis of Hirschsprung’s disease and bowel obstruction in the neonate.

Serum calcitonin measurements following stimulation by calcium or pentagastrin infusion reliably detect incipient MTC and may be used to select those MMN patients requiring thyroid surgery. Recognition of patients with the MMN syndrome and subsequent calcitonin screening and early surgical intervention will significantly reduce the chance of their developing terminal MTC. All MMN patients with mucosal neuromas or intestinal neurogangliomas should have such evaluations at least yearly. Relatives who are at risk for inheriting this dominant disease should be similarly evaluated, regardless of their normal appearance.

Introduction

The opportunity to recognize and evaluate the potential of malignancy based on an identifiable phenotype occurs infrequently in clinical medicine. However, certain conditions in which cancer may develop do have clinically definable characteristics, based on the presence of physical or biochemical markers. One example is the syndrome of multiple mucosal neuromas (MMN), in which patients may have associated medullary
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thyroid carcinoma (MTC), pheochromocytoma and a characteristic morphologic appearance. This report will emphasize the typical dysmorphic features and gastrointestinal symptoms which aid in the diagnosis of the MMN syndrome. This disease has been recently seen in a family and the present authors report the third instance of the MMN syndrome presenting as neonatal intestinal obstruction.5,12

Case Report

J. B. was hospitalized at the Shands Teaching Hospital, University of Florida, at two days of age because of intestinal obstruction. At surgery, a stenotic area of the descending colon was resected, sent for pathologic diagnosis and a colostomy was performed. Histology of the tissue showed increased neural elements in the myenteric plexi. Rectal biopsies obtained during this surgery demonstrated "plexiform ganglioneuromatosis," and the diagnosis of multiple mucosal neuromas was suggested. He was subsequently readmitted at the age of eight months for a colon biopsy, which confirmed the previous impression.

At age 21 months, the patient and his family were examined by the Genetics Service. In figure 1 is shown J. B.'s facial appearance which was similar to his mother's and characterized by patulous, thick lips, particularly the lower lip which also had several subcutaneous nodules. Several nodules were also located beneath the buccal mucosa. His face appeared elongated and the palate was high-arched. His mother's facial appearance was similar to, but more striking than, that of the patient. In addition, she had multiple subcutaneous nodules on her tongue, particularly the anterior border (figure 2). Her face had a coarse appearance (figure 3) and she had the arachnodactyly and tall stature typifying the Marfan syndrome-like habitus. Her history was remarkable for removal of bilateral pheochromocytomas and thyroid surgery for a "tumor." The patient's siblings, ages 7½ and 10 years, were normal in appearance and had normal ratios of upper to lower body segments.

J. B. was readmitted at age 2½ years for diarrhea and perineal excoriation. Pertinent laboratory studies on admission included normal electrolytes, BUN, creatinine, total protein, albumin, carotene, hematocrit, white blood cell count, triglycerides and stool cultures. Urinary excretion of vanilmandelic acid (VMA) was 3.0 mg per 24 hrs (normal 0.5 to 7.5) and homovanillic acid (HVA), 2.0 mg per 24 hrs (normal 0–15). Fasting serum calcitonin was 334 pg per ml (normal less than 400 pg per ml).11 A Pentagastrin stimulation test, using 0.5 μg per kg by IV push, resulted in serum calcitonin responses as follows: 5 min: 381; 10 min: 349; 15 min: 303; 30 min: 300 pg per ml (normal less than 400 pg per ml).11 A Pentagastrin stimulation test, using 0.5 μg per kg by IV push, resulted in serum calcitonin responses as follows: 5 min: 381; 10 min: 349; 15 min: 303; 30 min: 300 pg per ml (normal stimulated values less than 580 pg per ml; mean ± 2 S.D. of 220 ± 360 pg per ml).11 The diarrhea subsequently cleared and the family has refused either further testing or consideration of thyroidectomy.

Discussion

In 1961, Sipple16 reported a 14-fold increase in the frequency of adrenal pheochromocytoma among patients with carcinoma of the thyroid. Williams19 in 1965 showed that the thyroid carcinoma was of the medullary type originating in the parafollicular, calcitonin-producing cells (C-cells). Subsequent reports2,4,10,14 established that the multiple endocrine neoplasia (MEN) syndromes are familial and may show autosomal dominant inheritance.

In table I are shown the three major MEN syndromes and their associated lesions. MEN-1, or Wermer's syndrome, is comprised of lesions in the parathyroids, pancreatic islets, anterior pituitary and adrenal. In contrast, Sipple's syndrome, or...
MEN-2 or 2a, is characterized by pheochromocytoma and medullary thyroid carcinoma, in addition to parathyroid hyperplasia or adenoma.

The MMN syndrome is a variant of MEN-2 and has also been designated MEN-2b or MEN-3. It presents with mucosal neuromas over the eyelids, lips, tongue and buccal mucosa, associated with a medullary thyroid carcinoma and bilateral adrenal pheochromocytomas. These patients may also have thickened corneal nerves. The Marfanoid habitus is reported to occur in 83 percent of patients with the MMN syndrome and consists of tall, asthenic appearance, abnormal upper-to-lower body segment ratio and poor muscle development, with arachnodactyly, joint laxity and hypotonia. Additional anomalies may include kyphoscoliosis, pectus excavatum or carinatum, pes cavus, high arched palate and coarse facies features. Other features of true Marfan syndrome, such as aortic aneurysm and ectopia lentis, have not been described in the MMN syndrome.

The distinctive appearance aids in recognition of the diagnosis, as do the gastrointestinal manifestations resulting from abnormalities of the intestinal neural plexi. The intestinal ganglioneuromas (possibly more appropriately called neurogangliomas to indicate the predominance of neural tissue) are similar to the mucosal neuromas found in other locations in the MMN syndrome but are associated with functional abnormalities. They may cause symptoms simulating Hirschsprung's disease with megacolon and constipation or diarrhea. Symptomatic alimentary tract involvement was found to dominate the clinical presentation in 12 of the 16 cases of MMN syndrome reported by Carney et al.

In addition to the gastrointestinal manifestations and the distinctive phenotype, which may aid in the diagnosis of MMN, the family history may also be helpful. The majority of cases appear to arise by spontaneous mutation, but the remainder

Figure 2. Mother of patient J. B. Numerous subcutaneous nodules are located on the anterior border of her tongue.

Figure 3. Facial features of patient's mother. Elongation and coarseness of the face are apparent. Note also the left lateral thyroidectomy scar.
are inherited by an autosomal dominant mode.4,10,14 The presence of the completely developed phenotype in the parent of a suspected patient is invaluable in establishing the diagnosis.

The MMN syndrome is usually discernible during the first few years of life because of the more common phenotypic expressions mentioned previously. Our patient developed a large bowel obstruction on the second day of life, similar to both that in the neonate with MMN syndrome reported by Moyes and Alexander,12 and that in case No. 8 in the series of Carney et al.5 In addition, our patient was found to have a functionally "aganglionic" constricted segment of bowel identified at surgery. Various other gastrointestinal symptoms were present at or shortly after birth in 10 of the 16 cases reported by Carney et al.5 Bartlett2 reported a four-year-old male child who also had a positive family history and documented intestinal neurogangliomas but who presented with diarrhea. Other MMN patients reported with neurogangliomas have not presented with obstruction in the neonatal period.12,18 Ours is only the third such case and the first newborn to have demonstrated a gross anatomic lesion of the colon. These findings indicate that the development of intestinal neurogangliomas may frequently antedate the appearance of the other lesions associated with the MMN syndrome, including endocrine disease. The mucosal neuromas can also be present at birth, prior to development of pheochromocytomas or MTC.2 In newborns and older patients, the diffuse gastrointestinal neuroganglioma are always reported in association with mucosal neuromas;18 isolated intestinal ganglioneuromatosis, however, is not associated with MTC.7 These observations indicate that intestinal neurogangliomatosis may represent a variation of the mucosal neuroma component of the MMN syndrome.

Disturbances in gut motility, including diarrhea and constipation are common complaints in older patients with intestinal neurogangliomas associated with MEN-2 syndromes.2,5,18 These functional abnormalities may occur in the absence of radiographic evidence of diverticula and other bowel disease which are relatively common findings in patients with MTC.18 In the absence of demonstrable pathology, the diarrhea in some patients has been attributed to neuroactive compounds such as prostaglandin and serotonin,7 secreted by the tumor. The pheochromocytomas associated with the MMN syndrome may also cause diarrhea by production of epinephrine and/or norepinephrine,10 or vasoactive peptides.7 In contrast to older patients with MMN syndrome, the gastrointestinal symptomatology in the newborn usually consists of constipation and, occasionally, of obstruction, as in our patient. The relative infrequency of diarrhea in newborn patients with the MMN syndrome who do not yet have MTC suggests that the latter lesion is necessary for the development of diarrhea in the MMN syndrome. Chronic constipation and megacolon have been reported to predominate in a case of neurogangliomatosis and pheochromocytoma without MTC.9

The frequency of occurrence of intestinal neurogangliomatosis in the MMN

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**TABLE I**

Lesions in Multiple Endocrine Neoplasia (MEN) Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Lesions</th>
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<tbody>
<tr>
<td>MEN-1 (Wermer's Syndrome)</td>
<td>Parathyroid adenomas/hyperplasia</td>
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<tr>
<td></td>
<td>Pancreatic islet cell tumors</td>
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<td></td>
<td>Pituitary tumors</td>
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<td></td>
<td>Adrenal cortical adenomas</td>
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<td></td>
<td>Thyroid adenomas</td>
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<tr>
<td>MEN-2* (Sipple's Syndrome)</td>
<td>Medullary thyroid carcinoma</td>
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<tr>
<td></td>
<td>Pheochromocytoma</td>
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<tr>
<td></td>
<td>Parathyroid adenomas/hyperplasia</td>
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<tr>
<td>MEN-3† (Multiple Mucosal Neuroma Syndrome)</td>
<td>Medullary thyroid carcinoma</td>
</tr>
<tr>
<td></td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td></td>
<td>Mucosal neuromas</td>
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<td></td>
<td>Intestinal neurogangliomas</td>
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*MEN-2a††MEN-2b†
syndrome has been previously underestimated. Gorlin et al\textsuperscript{10} noted only one example in their analysis of 17 cases but suggest that this might be based on a limited assessment; recent estimates have been as high as 100 percent.\textsuperscript{3,5} The MMN syndrome itself may be more common than presently appreciated\textsuperscript{4} and, also based on our observations, should properly be included in the differential diagnosis of Hirschsprung's disease or intestinal obstruction, particularly in the new-born period.

The involvement of multiple endocrine and gastrointestinal sites in the MMN syndrome may have a unifying explanation. The tumors involved all arise from cells which Pearse\textsuperscript{13} has termed the "APUD" series (Amines Precursion Uptake Decarboxylase of L-aromatic amino acids). This term is used to mean that these cells have the capacity to take up precursors of biogenic amines and convert them to amine neurotransmitters through enzymatic decarboxylation.\textsuperscript{1} These cells also synthesize and secrete low molecular weight peptide hormones. The capacity of such cells to synthesize biogenic amines would thus seem to relate them to nervous tissue, and suggests that they are derived from neural crest tissue during embryogenesis. This has been shown to be the case for the C-cells from which MTC originates,\textsuperscript{13} and the medulla of the adrenal gland, where pheochromocytomas originate.\textsuperscript{7} A defect in the developing neural crest could lead to abnormalities in both sites. The finding of neuromas and intestinal neurogangliomas in the MMN syndrome is consistent with this hypothesis. The less frequent finding of parathyroid abnormalities in MMN syndrome than MEN-2a suggests that the parathyroid lesion may be a reactive hyperplasia secondary to chronically high calcitonin levels and not the result of a primary defect in the embryologic neural crest.\textsuperscript{3}

Since MTC is a neoplasm involving the C-cells of the thyroid gland, the tumor produces abnormally large quantities of calcitonin.\textsuperscript{7} In most patients with MTC, basal levels of calcitonin are sufficiently elevated to be diagnostic. In fact, the radioimmunoassay for calcitonin can establish the presence of MTC with such a high degree of accuracy that it is probably the most clinically reliable serologic test for the diagnosis of cancer.\textsuperscript{7} Unfortunately a significant percentage of patients with MTC have basal calcitonin levels which are indistinguishable from normal. Also, the levels in any one patient may be only intermittently abnormal. Many cases of intermittently high levels may represent early stages in the development of the tumor or even C-cell hyperplasia, either of which one would like most to diagnose since they are amenable to surgical cure.\textsuperscript{7} Provocative testing decreases the incidence of false negative diagnosis\textsuperscript{17} and takes advantage of the fact that the tumor is not autonomous. Secretion of calcitonin by C-cells in MTC is stimulated by hypercalcemia and other secretagogues.

One of the first agents to be used for the stimulation of calcitonin secretion was glucagon, but its effect was variable and unreliable. In addition, in patients with associated pheochromocytomas, glucagon can cause the release of catecholamines and precipitate an adrenergic crisis.\textsuperscript{7} Calcium infusions, particularly the recently described short term procedures, reliably stimulate calcitonin secretion, despite an elevation in the plasma calcium of less than 1 mg per dl. Side effects caused by hypercalcemia, such as hypertension, nausea and vomiting, have been substantially reduced by the abbreviated procedures. Another widely used stimulus to calcitonin secretion in MTC patients is pentagastrin, 0.5 μg per kg IV, which appears to be as effective as calcium infusion as a calcitonin secretagogue. The response to both agents appears dependent on the rapidity of infusion.\textsuperscript{7} Either pentagastrin or calcium tests will define the presence of tumor in most instances, but false negatives occur with both procedures.\textsuperscript{7,11} Thus, when there is clinical suspicion of MTC and one procedure
gives negative results, the alternative procedure should be used before excluding the diagnosis.

Earlier estimates of approximately 50 percent for the frequency of MTC in patients with MMN were undoubtedly too low and the true incidence is probably close to 100 percent. In addition, the development of the thyroid carcinoma component of the MMN syndrome, usually reported to be between 18 and 25 years, has recently been reported as early as ten years. Moreover, the neonate reported to be between 18 and 25 percent for the frequency of MTC in patients with MMN were undoubtedly too low and the true incidence is probably close to 100 percent. In addition, the development of the thyroid carcinoma component of the MMN syndrome, usually reported to be between 18 and 25 years, has recently been reported as early as ten years. Moreover, the neonate recently reported by Moyses and Alexander had a resection of a medullary thyroid carcinoma at 15 months of age. Markedly elevated calcitonin levels were measured at the age of eight months in their patient.

Early death in patients with the MMN is related to development of MTC. Graze et al have demonstrated the effectiveness of a calcitonin screening program for detecting familial MTC in a premetastatic stage. Measurement of calcitonin after calcium or pentagastrin provocation offers a reliable means of detecting this thyroid malignancy even during its hyperplastic, pre-malignant stages. Serial measurements of calcitonin following stimulation may be used to select those patients requiring surgery, and early surgical intervention in those MMN patients with positive calcitonin screening tests will prevent the development of fatal medullary thyroid carcinoma. All patients with mucosal neuromas or intestinal neurogangliomas should have calcitonin levels monitored at least yearly. Since an occasional MMN patient has no abnormalities of the face, oral mucosa or skeletal system, family members who have a chance of inheriting the gene for this dominant disease should have the same evaluation despite their normal appearance.

References