Familial Endocrine Tumors

MULTIPLE ENDOCRINE NEOPLASIA (MEN) syndromes, so clearly and concisely reviewed by Pont in this issue's Medical Progress section, are of special interest for many reasons, one being that unlike most endocrine tumors, these syndromes are familial. Since the discovery that there is a genetic predisposition for the development of one or more endocrine neoplasms, these syndromes have been the subject of extensive and rewarding study.

Although much remains to be learned about the pathogenesis of these tumors, several interesting observations have been made. Using as cell markers the electrophoretic pattern of glucose-6-phosphate dehydrogenase (G-6-PD), an X-linked isoenzyme, Baylin and co-workers have examined tissues from patients with medullary thyroid carcinoma and pheochromocytoma.[1,2] In females heterozygous for the A and B isoenzymes of G-6-PD, inactivation of one X chromosome, which occurs randomly during embryonic development, results in two cell populations in every tissue, one producing type A isoenzyme and the other type B. These investigators found only one isoenzyme in a given tumor, which indicated that the tumor arose from a single clone of susceptible cells and not from multiple cells. In one patient with medullary carcinoma, tissue from the tumor in the left lobe of the thyroid contained only type A isoenzyme and tissue from the tumor in the right lobe, only type B. Because in different tumors in this same patient there were different G-6-PD isoenzymes, the investigators proposed that neoplasms in the MEN II syndrome arise from two mutational events—an initial inherited mutation produces multiple clones of susceptible cells and a final mutation in one clone of these cells results in tumor formation. The nature of the factor or factors that produce the final mutation remains unknown and may be distinct for each organ. Moreover, there is a growing body of information supporting the concept that in multiple endocrine neoplasia, hyperplasia precedes neoplastic transformation. The progression of hyperplasia to malignant lesions is most clearly documented in medullary carcinoma, although the chronologic position of hyperplasia in this postulated sequence of tumorigenesis has not been clarified. The disparity in neoplastic transformation to medullary carcinoma (a malignant tumor in the thyroid) and to pheochromocytoma (a tumor which is usually benign in the adrenal) of cells that share the same basic inherited defect is another intriguing aspect of this syndrome.

Of immediate importance in the care of patients and families with multiple endocrine neoplasia are the advances that have been made in early diagnosis and treatment of these syndromes, especially MEN II (medullary carcinoma, pheochromocytoma and hyperparathyroidism). The immense progress that has been made in understanding and treating this syndrome serves as a stimulus in the continuing search for biochemical markers for other tumors. To give a sense of perspective, a brief review of some of the accomplishments in the study of this disease over the past 20 years is in order.

In 1959 medullary carcinoma was recognized as an entity distinct from other types of thyroid cancer. In the 1960's the following strides were made: a strong familial tendency and a frequent association with pheochromocytoma and hyperparathyroidism were noted; the cellular origin of the tumor from the parafollicular or C cells was established, and a highly specific and sensitive biochemical tumor marker, calcitonin, was identified. In the 1970's the measurement of calcitonin in peripheral blood by radioimmunoassay proved to be of extreme value in the diagnosis of medullary carcinoma and management of patients. Calcitonin levels, basal and stimulated, have permitted detection of occult tumors much earlier than was possible with conventional diagnostic techniques, such as palpation and radioisotope scanning, that have been applied to evaluating tumors of the thyroid. Early detection of medullary thyroid carcinoma has resulted in fewer patients having metastasis to regional lymph nodes at the time of surgical operations. Prognosis has been improved, and cure is now possible.

The potential benefits of early detection of medullary carcinoma justify an aggressive approach to screening patients known to be at increased risk. The basic defect is inherited as an autosomal dominant trait with a high degree of penetrance, so that approximately 50 percent of a patient's siblings and children will, therefore, be affected. In addition to annual testing of all family members of patients with MEN II, initial family screening appears warranted in patients

with medullary carcinoma presumed to be sporadic. Sizemore and co-workers surveyed 219 primary relatives (siblings and children) of 36 patients with medullary carcinoma and no family history of thyroid tumor, pheochromocytoma or hyperparathyroidism, and identified 57 affected members in seven families.[3] Because not all relatives were tested, the frequency of familial medullary carcinoma in patients with tumors presumed to be sporadic on the basis of the patients' histories is probably higher than the 19 percent reported. Calcitonin testing should also be carried out in all patients in whom the diagnosis of pheochromocytoma is made and in anyone found to have hyperparathyroidism due to multiple gland involvement. Initially, it appeared that elevated calcitonin levels were diagnostic of medullary thyroid carcinoma. Subsequently, however, ectopic production by a variety of tumors has been reported, and, occasionally, elevated calcitonin levels occur in nonmalignant disorders. Although this possibility must be considered, the clinical presentation usually permits these conditions to be easily excluded.

Screening tests for patients and families with MEN I (hyperparathyroidism, islet cell tumors and pituitary adenomas), as indicated in Dr. Pont's paper, are complex. As with any test, interpretation is best accomplished when correlated with a patient's clinical presentation. The diagnosis of hyperparathyroidism, even though asymptomatic, presents little difficulty and the vast majority of patients with functioning islet cell tumors have characteristic symptoms. Diagnostic problems may, however, be encountered in early detection of pituitary tumors. Prolactin measurements have proved to be extremely valuable in the diagnostic study of patients with suspected pituitary tumors. Antunes and colleagues studied the cases of 47 patients with nonfamilial pituitary tumors.[4] Serum prolactin concentration was elevated in 79 percent. Even when patients with galactorrhea were excluded, hyperprolactinemia was present in more than 65 percent. Although experience with prolactin determinations in the MEN I syndrome is limited, it is very likely that a similar prevalence of hyperprolactinemia will be found.

Initial evaluation of high-risk patients should include examination of visual fields and tomography of the sella turcica. If findings from either are abnormal, pituitary function should be assessed in women with galactorrhea, oligomenorrhea or amenorrhea, and in men with impaired libido or potency. While tomograms of the sella turcica are superior to plain films in diagnosing early pituitary tumors, their interpretation remains controversial.[5] A sella turcica with slight asymmetry or with a double floor should not be considered pathologic unless associated thinning or erosion of the lamina dura or destruction of bony structures is present. The accuracy of radiologic diagnosis of pituitary tumors is improved when endocrine studies corroborate. In the absence of pituitary hormone hypersecretion as reflected by peripheral blood hormone levels, or hypopituitarism confirmed by abnormal response to stimulation tests, the diagnosis of a pituitary tumor by sella tomography alone is tenuous. The growth of pituitary adenomas is slow. If findings of initial screening studies are within normal limits, it is usually not necessary to reevaluate pituitary status more frequently than every two or three years. Because of potential cataract formation related to cumulative radiation, follow-up tomograms of the sella turcica should be ordered judiciously.

The information obtained from the study of patients with multiple endocrine neoplasia syndromes has importance for practicing physicians and investigators alike. By applying the tests, as clearly outlined in the review, early diagnosis and treatment of tumors that would otherwise be lethal is now possible. The success of using biochemical markers for the detection of tumors should encourage more extensive investigations of this kind.

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