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Minireview

Inherited endocrinopathies: An update

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ABSTRACT

Inherited endocrinopathies, including multiple endocrine neoplasia type 1 (MEN-1), multiple endocrine neoplasia type 2 syndromes (MEN-2A, MEN-2B, familial medullary thyroid carcinoma), and inherited syndromes with pheochromocytoma (von Hippel–Lindau disease, neurofibromatosis type 1, others), comprise a heterogeneous group of cancer susceptibility syndromes that affect one or more components of the endocrine system. During the past several years, novel findings regarding genotype–phenotype correlation have highlighted the importance of establishing a genetic diagnosis in the treatment of these diseases. Here, we present a case-based review of recent advances in the genetics, diagnosis and management of inherited endocrinopathies.

Genetic alterations play a central role in the development and progression of cancer. In sporadic malignancies, acquired (somatic) mutations predominate. Cancer susceptibility syndromes, in contrast, are characterized by inherited (germ-line) mutations and generally exhibit autosomal dominant patterns of inheritance. Multiple endocrine neoplasia type 1 (MEN-1), multiple endocrine neoplasia type 2 syndromes (MEN-2A, MEN-2B, familial medullary thyroid carcinoma), and inherited pheochromocytoma syndromes (von Hippel–Lindau disease, neurofibromatosis type 1, others) are examples of such syndromes. In this review, we discuss a series of patients recently treated by our multidisciplinary endocrine surgical unit. Each case illustrates current controversies and/or novel applications of basic research in clinical management.

MEN-1

Clinical manifestations

MEN-1 is an autosomal dominant syndrome characterized by parathyroid adenomas, pancreaticoduodenal neuroendocrine tumors and pituitary adenomas. The clinical diagnosis of MEN-1 is made when two of these three endocrine tumors occur in the same patient. Infrequently, patients may also develop bronchial, gastrointestinal and thymic carcinoids, benign adrenocortical and thyroid tumors, lipomas, facial angiofibromas, dermal collagenomas, and ependymomas of the central nervous system. The occurrence of clinical signs and symptoms, in order of decreasing frequency is: hypercalcemia, nephrolithiasis, peptic ulcer disease, hypoglycemia, visual field loss, hypopituitarism, acromegaly, galactorrhea–amenorrhea, and rarely Cushing's syndrome [1]. Patients with MEN-1 have a decreased life expectancy, with a 50% probability of death by age 50, and one half of MEN-1 patients die as a result of a malignant tumoral process or sequela of the disease [2–4].

Case 1

A 15-year-old male presents with rapid weight gain of 5–10 pounds per month over the course of two years, resulting in a total weight increase of 142 pounds. Laboratory testing reveals an elevated serum cortisol of 32 μg/dL (nl 5–25 μg/dL), and elevated serum adrenocorticotropic hormone (ACTH) of 97 pg/mL (nl 20–80 pg/mL). Subsequent inferior petrosal sinus sampling shows a central ACTH gradient. The patient is diagnosed with Cushing's

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disease and undergoes *trans*-sphenoidal pituitary microsurgery with removal of an ACTH-producing adenoma. The cortisol levels normalize and the patient improves.

Pituitary disease

Anterior pituitary tumors develop in approximately 65% of patients with MEN-1 [5]. The order of frequency in which these pituitary tumors occur, beginning with the most frequent, is as follows: prolactinoma, growth hormone-secreting tumor, nonfunctional tumor, and rarely adrenocorticotropic hormone or thyroid stimulating hormone-secreting tumors [1]. Every type of anterior pituitary adenoma, except true gonadotropinoma, has been reported in MEN-1. About two thirds of tumors are microadenomas. Tumors may present with mass effect or hormone excess. Treatment of pituitary tumors in MEN-1 varies according to the type of the adenoma and is identical to that in sporadic pituitary tumors.

Case 1, continued

The patient is subsequently found to have an elevated serum calcium of 10.9 mg/dL, and undergoes removal of an enlarged right inferior parathyroid gland approximately 9 months after his initial surgery for Cushing's disease. Postoperatively, the patient's calcium is noted to have increased to 11.3 mg/dL. An ultrasound of the neck shows two enlarged parathyroids (Fig. 1). The clinical diagnosis of MEN-1 is made, and the patient undergoes re-do parathyroidectomy at a tertiary referral center. Intraoperative findings are significant for a markedly enlarged right superior parathyroid adenoma (1750 mg, normal <45 mg), a moderately enlarged left superior parathyroid adenoma (120 mg), a moderately enlarged left inferior parathyroid adenoma (150 mg), and no right inferior parathyroid (likely excised during prior operation). No macroscopic ectopic parathyroid tissue is identified in the thymus or inferior paratracheal spaces. Twenty-five mg of healthy appearing parathyroid tissue is implanted into the brachioradialis muscle of the non-dominant forearm.

Parathyroid disease

Asymptomatic multigland hyperparathyroidism is the most common and usually earliest feature of MEN-1. Penetrance reaches nearly 100% by age 50, with typical age of onset between 20 and 25 years. Independent parathyroid adenomas arise due to impaired or loss of function of the menin tumor-suppressor protein (see below). It is important to note that hyperparathyroidism (HPT) in MEN-1 is due to clonal proliferation arising from inactivation of the *MEN1* gene, rather than a uniform cellular response to humoral stimuli [6]. Surgery remains the primary treatment, either by total four-gland parathyroidectomy with autotransplantation of parathyroid tissue to the forearm, or by subtotal (three-and-one-half-gland) parathyroidectomy, leaving one parathyroid remnant in situ on an intact vascular pedicle. Because these operations carry substantial (5–10%) risk of postoperative hypoparathyroidism, parathyroid tissue may be cryopreserved to permit a subsequent autograft procedure. By 8–12 years after successful subtotal parathyroidectomy in MEN-1, HPT will have recurred in 50% of euparathyroid cases [7]. This and the young age at initial operation result in frequent parathyroid reoperations characteristic to MEN-1. Calcium-sensing receptor agonists (calcimimetics), a new class of drugs, can act directly on the parathyroid gland, decrease parathyroid hormone (PTH) release, and perhaps even decrease tumor growth. They are presently under investigation as a possible noninvasive treatment of HPT in MEN-1 [8,9].

Case 1, continued

A surveillance MRI of the abdomen and pelvis (Fig. 2) shows multiple enhancing lesions in the pancreas. The two largest are in the pancreatic head, measuring 3.2×3.7 cm, and 4×3.8 cm, respectively. At least four smaller lesions, measuring approximately 0.5–1 cm each, are seen in the pancreatic body and tail. The patient undergoes pancreaticoduodenal (Whipple) resection.

Pancreatic endocrine disease

The prevalence of pancreatic neuroendocrine tumors (PNETs) in MEN-1-affected individuals varies in different clinical series from 30% to 75% [7]. The lesions are characteristically multicentric and range from microadenomas, to macroadenomas, to invasive and metastatic carcinomas [10]. The lesions arise in any part of the pancreas, or as foci throughout the duodenal submucosa. Tumors producing pancreatic polypeptide are the most common PNETs. These tumors are clinically nonfunctional and cause symptoms by way of the tumor mass itself. Functional PNETs occur with the

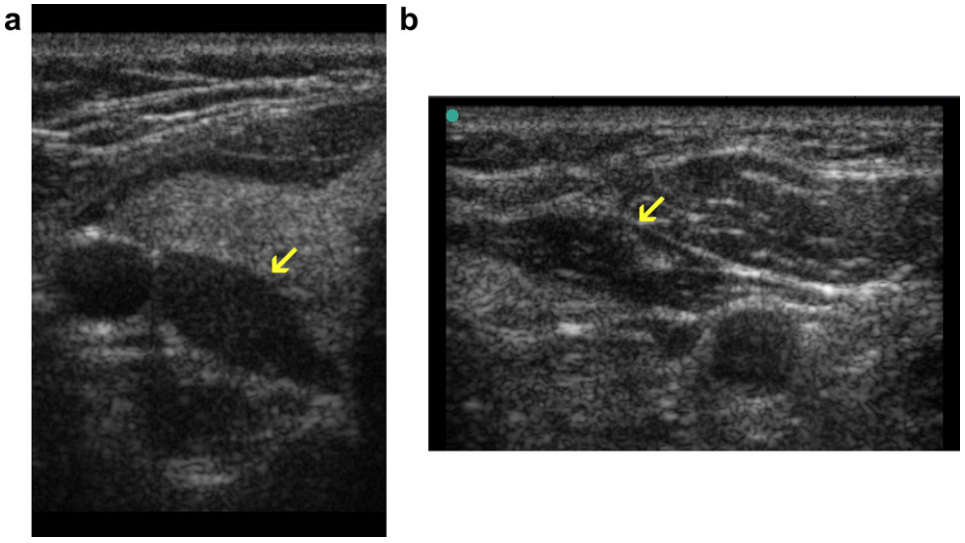

Fig. 1. Shown here are the ultrasound images which demonstrate enlarged parathyroid glands (arrows), one measuring more than 2 cm in diameter associated with the right superior position (a), and the other measuring approximately 0.75 cm in the left inferior position (b).