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HEREDITARY SYNDROMES PREDISPOSING TO ENDOCRINE TUMORS AND THEIR SKIN MANIFESTATIONS

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Abstract

We often think of the lentiginoses, phacomatoses and other neurocutaneous syndromes as conditions that affect the skin and also predispose to a variety of tumors. However, we rarely think of Peutz-Jeghers syndrome (PJS), Carney complex (CNC), Cowden disease (CD), neurofibromatosis type-1 (NF-1) or tuberous sclerosis (TSC) as conditions that are multiple endocrine neoplasias (MEN). Indeed, all of these conditions predispose to a variety of endocrine tumors, in additions to many other neoplasms. On the other hand, the classic MENs, type 1 and 2 (MEN-1 and MEN-2, respectively) are almost never thought in terms of their skin manifestations. In this review, we present extensively the MEN-1, MEN-2 and PJS syndromes, and briefly refer to CD, NF-1, and TSC. CNC is discussed in another article in this journal issue.

Keywords

Multiple endocrine neoplasia; hereditary tumor syndrome; Peutz-Jeghers syndrome; Cowden disease; neurofibromatosis type 1; tuberous sclerosis

MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 (MEN-1)

Etiology/Pathophysiology

Familial MEN-1 is an autosomal dominant disorder with variable penetrance characterized by tumors of the parathyroids, anterior pituitary, pancreas, and other locations of the gastrointestinal tract, and other tissues. The *MEN1* gene which codes for the protein *menin* is located on chromosome 11q13 and was first identified in 1997 (1). Individuals affected by MEN-1 inherit a *menin* inactivated allele (first hit); tumorigenesis in specific tissues follows inactivation of the remaining normal allele (second hit). MEN-1 is regarded as an endocrinopathy presenting in young adulthood. (2) As with many hereditary tumors, MEN-1 typically presents earlier than sporadic tumors of the same tissue type. The age disparity at presentation is striking for MEN-1-related hyperparathyroidism (third versus sixth decade in

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Compliance with ethical standards

Conflict of interest

The author declares that he has no conflict of interest.

sporadic cases) but less pronounced for gastrinoma and insulinoma (fourth versus fifth decade in each). (3) By contrast, there has been no apparent age difference for the onset of MEN-1-associated and sporadic prolactinoma (fourth decade) (4–5). The age of clinical onset of treatable MEN-1-related tumors is an important factor in formulating biochemical and DNA screening recommendations.

Clinical Presentation

Hyperparathyroidism is usually the earliest and most common endocrine manifestation of MEN-1, with hypercalcemia being an almost universal finding at the time of MEN-1 diagnosis; clinically evident hyperparathyroidism in MEN-1 has been reported at ages 5 and 7 years and several times at age 8 years (1–4). However, no morbidity has been reported from early hyperparathyroidism in MEN-1. MEN-1-associated prolactinomas have been reported previously in children aged 10–13 years and growth hormone (GH)-producing adenomas in MEN-1 have been described as early as in a 5-year-old boy (5). Gastrinoma, the other defining feature of MEN-1 has not been seen earlier than age 12, whereas MEN-1-related insulinoma has been described as early as age 6 (1–4).

Cutaneous manifestations of MEN-1

Patients with MEN-1 have angiofibromas, collagenomas, lipomas and various macules (6–12). Facial angiofibromas are diagnostic of MEN-1 at an early age and may be used for the detection of carriers at an early age within a family that already known to be affected with MEN-1 (6, 11). Melanoma and squamous cell carcinoma may occur coincidentally (13).

Diagnosis

A diagnosis of MEN-1 is made when either: 1. A patient has 2 or more MEN-1-associated lesions, or 2. A patient has only one lesion, but there exists a family history of relatives with MEN1; or 3. A patient has a positive genetic test for an abnormal *MEN1* sequence, a mutation or a defect that has previously been associated with the disease in other individuals (14–16).

As mentioned above, there are three main types of lesions associated with MEN-1: Parathyroid glands hyperplasia or adenomas, tumors of the endocrine pancreas and gut (duodenum), and pituitary adenomas. Roughly 80% (8 in 10) of patients with MEN1 will have developed at least one of these tumors by the age of 50, and around 40% (4 in 10) by the age of 20 years. The condition varies greatly even within families; not everyone will have the same tumors and they will not occur at the same age.

Screening/Monitoring

Patients with known MEN-1 should be screened annually, starting in childhood (after the age of 5 years), for the main manifestations of the disorder (15, 16). Careful monitoring of the growth rate and annual screening of plasma ionized calcium and serum intact parathyroid hormone (i-PTH) in children of families with MEN-1, who are known mutation carriers is recommended. If the growth rate is increased as in acromegaly, or decreased as in prolactinomas, Cushing disease, or Cushing syndrome, appropriate tests are ordered. The latter tumors can also be associated with an increase in weight gain. Routine screening for

pituitary tumors in the absence of symptoms is not necessary until late childhood or early adolescence (ages 10–15 years) because they occur only rarely before these ages. Similarly, fasting gastrin, C-peptide, and plasma insulin determinations and serial prolactin measurements (obtained every 20 minutes for 1 hour through an indwelling catheter that has been inserted an hour before the sampling to avoid stress-related, falsely elevated levels) and pituitary or abdominal imaging are not necessary until adolescence. Although such biochemical testing may be done annually thereafter, imaging may be done only as needed and when the presence of a tumor is suggested by clinical symptoms or laboratory testing; clinical symptoms such as hypoglycemia, delayed puberty, irregular menses, gynecomastia, galactorrhea, weight gain, moon facies, hirsutism, abnormal visual fields, decrease in school performance, suggest a pituitary tumor and should be followed by an MRI of the pituitary with gadolinium. Depending on the size of the pituitary tumor, symptoms of secondary adrenal insufficiency may also be present. If hypoglycemia or peptic ulcer disease are the presenting symptoms, abdominal imaging is necessary to screen for insulinoma and gastrinoma, respectively; however insulinomas and gastrinomas are extraordinarily rare in children with MEN-1. In young adults with MEN-1, in addition to the annual biochemical testing prescribed earlier, annual imaging of the abdomen (and the pancreas in particular) may be obtained; pituitary imaging may be obtained in the absence of symptoms or suggestive biochemical testing no more frequently than every 5 years to avoid false-positive studies and unnecessary follow-up testing.

Molecular Genetics and Recommendations for Screening

The identification of the *MEN1* gene led to mutation testing that is now available at several centers (1–4, 14–16). The main candidates for *MEN1* mutational analysis include the index cases with MEN-1, their unaffected relatives, and some cases with features atypical for MEN-1. There have been several hundreds of mutations in *menin*; they are spread almost equally along the length of the gene without any apparent genotype–phenotype correlation. Some mutations occur more frequently than others, but there are no obvious “hot spots” in the nine coding exons of the gene (14–16). The mutations that are more frequent involve exons 83, 84, 209–211, and 514–516, which contain unstable DNA sequences (e.g., dinucleotide repeats or poly(C) tracts). A small number of MEN-1 kindreds do not have mutations in the *MEN1* gene but rather 11q13 deletions; others have mutations in other genes. The recent recognition of significant morbidity from MEN-1 at young ages (5), the need for carrier testing in large families with known mutations, and advances in molecular testing will probably lead to more frequent genetic testing in the future.

Treatment

The treatment of tumors associated with MEN-1 in children is mainly surgical, with the exception of prolactinomas and the medical management of Zollinger–Ellison syndrome (ZES) (1–4, 14–16). Gigantism may be treated by somatostatin analogues and dopamine agonists as in adult patients with similar tumors, but the primary approach would be by transsphenoidal surgery (TSS). Orally administered dopamine agonists are the main treatment for prolactinomas, and only occasionally may a macroprolactinoma that is not responsive to medical treatment and causes symptoms or continues to grow need to be excised by TSS. Medical gastrectomy by omeprazole or ranitidine and other proton-pump

inhibitors or H₂-blockers, respectively, is all that is required for the treatment of hypergastrinemia. Surgery should be avoided as the primary treatment of ZES. Hyperparathyroidism is treated surgically if a serum calcium level consistently above 12 mg/dL or when nephrolithiasis or bone loss is evident. Other tumors associated with MEN-1 that are symptomatic or have the potential of being malignant, such as insulinoma or the rare case of a malignant gastrinoma, are also approached surgically.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2

Etiology/Pathophysiology

The MEN-2 syndromes are the phenotypic expressions of variants of activating mutations in the *RET* proto-oncogene, a tyrosine kinase receptor (17–27). All clinical manifestations of the MEN-2 syndromes reflect the inappropriate transduction of this growth- and survival-promoting signal in the neural crest–derived tissues that naturally express *RET* (17, 18). The primary and most common lesion of the MEN-2 syndromes is medullary thyroid cancer (MTC) (22); it is present in up to 95% of patients with MEN-2 and is preceded by hyperplasia of the calcitonin-secreting thyroid parafollicular C cells (20). Histological evidence of MTC in more than 95% of obligate gene carriers is present by age 35 years. Calcitonin provocative testing is not as specific for MTC as was believed initially because a small fraction of persons with normal calcitonin provocative testing were shown to be obligate noncarriers of their kindred's characteristic *RET* mutation. Conversely, those classified as being affected on the basis of C cell hyperplasia alone should be reevaluated with *RET* testing to allow accurate counseling about their children's risk for MEN-2 (17–23).

Clinical Presentation

Pheochromocytoma typically affects 50% to 60% of MEN-2A kindreds with a high rate of bilaterality but a low rate of extra-adrenal sites or malignancy (17–27). The tumor is commonly present in MEN-2B and absent by definition in familial medullary thyroid cancer (FMTTC). A yearly program for pheochromocytoma that uses urinary catecholamines and metabolites to screen can effectively identify tumors at an early stage (<2 cm), before the development of hypertension or other adverse sequelae. Laparoscopic adrenalectomy is now the method of choice for the surgical removal of a pheochromocytoma.

Parathyroid disease is detected clinically in 10% to 15% of patients with MEN-2A (17–27). Recently, two variants of MEN-2A with distinctive nonendocrine manifestations have been recognized. MEN-2A with cutaneous lichen amyloidosis, which is characterized by pruritic lesions composed of subepidermal keratin deposits over the scapular region¹⁴⁷, and MEN-2A with partial or extensive Hirschsprung syndrome, which represents another distinct clinical syndrome. Patients with this disease exhibit evidence of both *RET* hyperfunction and hypofunction in a tissue-specific fashion.

Expanding the clinical spectrum of the MEN-2 syndromes are the distinctive skeletal findings found in virtually all MEN-2B patients: elongated facies with a long, relatively thin nose, proliferation of corneal nerves, mucosal neuromas of the lips and tongue, and

gastrointestinal ganglioneuromas (22, 23). In addition, these patients frequently have aggressive tumors, both MTC and pheochromocytoma. These manifestations all appear to stem from abnormal proliferation of neural crest elements during fetal and postnatal life and may be orchestrated by a hyperfunctioning *RET* tyrosine kinase receptor.

Cutaneous manifestations of MEN-2

Patients with MEN-2 may present with lichen amyloidosis (Figure 1) (28, 29). Patients with MEN2B have a distinct Marfanoid habitus and mucosal neuromas are often obvious in the oral area and the lips (22).

Diagnosis

Diagnosis of MTC is made by genetic testing (in the familial setting, see below), a palpable neck mass (or masses) and/or elevation of calcitonin levels (20–23, 30, 31). MTC is frequently the first neoplastic manifestation in MEN2A patients, with MTC occurring as early as in the first 5 years of life. In families without an established diagnosis of MEN2A, patients typically present with a neck mass between the ages of 15 and 20 years. MEN2A accounts for 70% to 80% of individuals with hereditary MTC. Occasionally, a patient may present with one of the two rare variants of MEN2A, the one with Hirschsprung's disease (24) and the other with cutaneous lichen amyloidosis and MTC (26) is found in the work-up. The second inherited subtype of MTC, MEN2B, accounts for only 5% of hereditary MTC cases. MEN 2B is characterized by clinically aggressive MTC, pheochromocytoma, a Marfanoid body habitus, mucosal (and other) neuromas, and intestinal tumors (mostly ganglioneuromas); these patients typically do not manifest hyperparathyroidism. The third inherited subtype of MTC is familial MTC (FMTC). This subtype accounts for 10% to 20% of hereditary MTC cases; only the thyroid gland is affected typically in these patients, although rare large families with both MEN2A and FMTC also exist. In general, FMTC patients present later with MTC than those with MEN2A or MEN2B, usually between 20 and 40 years of age.

Screening/Monitoring

In known carriers of a *RET* mutation, other than prophylactic thyroidectomy (see below), annual screening for pheochromocytoma should be performed after age 5, along with a serum ionized calcium measurement; usually hyperparathyroidism in these patients does not develop until later childhood or adolescence, so, if necessary, one can limit the screening to that for pheochromocytoma *only* between the ages 5 and 10 years. Plasma catecholamines are the best screening test for pheochromocytoma (see below). An ionized calcium level that is elevated should be followed by measurements of parathyroid hormone.

Molecular Genetics and Recommendations for Screening—Analyzing the *RET* gene in the MEN-2A and FMTC syndromes revealed that most of the patients had mutated one of five cysteine codons in exons 10 and 11; however, isolated FMTC also was caused by mutations in the first tyrosine kinase domain of the receptor (18, 20). The cysteine-to-arginine change in codon 634 of the *RET* protein appears to be the most common mutation in the MEN-2 syndromes and is also found in the few kindreds with MEN-2A that have pheochromocytoma and hyperparathyroidism but no other clinical manifestations. In

MEN-2A/Hirschsprung disease, most kindreds have mutations in codons 609, 618, and 620. In MEN-2B, the mutations are in the tyrosine kinase domain.

Over the past 35 years, there has been a substantial improvement in survival in MEN-2 families, an improvement largely attributable to the success of family screening programs, first provocative biochemical tests, and more recently, detection of *RET* gene mutations (30–33). *RET* gene analysis has superseded older methods because of its high sensitivity and specificity, utility in younger children, and much higher degree of patient acceptance. A typical screening program for known MEN-2A and FMTC kindreds is to initiate testing for *RET* mutations at 2 years of age. In the case of MEN-2B, it is generally possible to recognize the characteristic mucosal neuroma phenotype within the first 2 years of life. Prophylactic thyroidectomy is now recommended for all patients who test positive for most disease-causing mutations of the *RET* gene. In addition to established MEN-2 kindreds, 6% to 8% of MTC patients with no apparent family history of the disorder harbor germline *RET* mutations and thus may have offspring at risk. On the basis of this figure, it appears prudent to offer germline *RET* analysis to everyone with apparent sporadic MTC.

Treatment

Other than prophylactic thyroidectomy, most other tumors associated with MEN-2 are also treated surgically (30–32). As in MEN-1, hyperparathyroidism is treated surgically when necessary (see above) by near-total parathyroidectomy (or by total parathyroidectomy and reimplantation of parathyroid tissue in the nondominant forearm). The rate of recurrent hypercalcemia is less in MEN-2 than in MEN-1 after these procedures but does not differ substantially between them. Pheochromocytomas are removed preferably laparoscopically today.

PEUTZ-JEGHERS SYNDROME

Etiology/Pathophysiology

The hallmark of this syndrome is the presence of pigmented spots on the lips, which are first present in early childhood (34–39). These lesions are associated with gastrointestinal hamartomatous polyps (38, 39). Gastrointestinal cancers are frequent in Peutz-Jeghers syndrome (PJS) (35–37); they may arise from genetic changes known to occur in colorectal carcinoma and other tumors because the PJS-responsible gene, *STK1/LKB1*, functions as a tumor suppressor (37). PJS patients are also at an increased risk for breast, ovarian, testicular, uterine, and cervical cancers, as well as nonmalignant lesions in these tissues; the overall incidence of carcinoma in patients with PJS varies from 20% to 50%, and it appears at a relatively early age (36, 37, 41).

Endocrine tumors are also frequent in PJS (42, 43). These include thyroid nodules and cancer and genital tract neoplasms. The latter include, in female patients with PJS, ovarian neoplasms from both the epithelium and stromal cells and adenoma malignum of the cervix and adenocarcinoma of the endometrium. Male patients with PJS often have Leydig cell tumors or a Sertoli cell tumor that is uniquely found in PJS and in Carney complex (CNC) (44, 45): large cell calcifying Sertoli cell tumor (LCCSCT). LCCSCT in PJS, as in CNC,

may be associated with increased aromatization of adrenal or testicular androgens, which produces estradiol and other estrogens (estrone, in particular) that may lead to precocious puberty and prepubertal or peripubertal gynecomastia (45).

Clinical presentation

Most patients with PJS present in childhood with complications of polyps (i.e., bowel obstruction). Peri-oral and mucosal pigmentation may also attract attention and lead to diagnosis at an early age. Both polyps and pigmented spots and other skin pigmentation defects become apparent before puberty, typically after the age of 5 years. Occasionally, the first manifestation in boys is gynecomastia due to LCCSCT.

Cutaneous manifestations of PJS

Patients with PJS may present with multiple lentigines with intense coverage of the lips and the peri-oral area (34, 38); a variety of other pigmented lesions are common (Figure 2).

Diagnosis

Diagnosis of PJS is made when at least one of the classic stigmata of the disease is present and/or if there is family history (34). Diagnosis is confirmed by molecular testing for *STK11/LKB1* mutations and/or deletions (see below).

Molecular Genetics—Most PJS families have been linked to 19p13.3; the PJS gene at 19p13.3 is *STK11* (for serine threonine kinase 11) also known as *LKB1* (34–37, 40). More than half the families with PJS have mutations in this gene, although the percentage varies greatly from one study to the next. *STK11/LKB1* is a novel serine–threonine kinase containing nine exons; The kinase domain of the *STK11/LKB1* gene is highly conserved between mouse and human (34). Although it has been suggested that mouse Lkb1 is a nuclear protein, wild-type *STK11/LKB1* shows both nuclear and cytoplasmic localization. A number of recent studies have elucidated the effects of inherited *STK11/LKB1* mutations in PJS kindreds based on the functional domains of the protein; in most cases, elimination of the kinase activity underlies the molecular cause of the phenotype (36, 37).

Treatment & Prognosis

Tumors associated with PJS are surgically removed, as needed. Patients need to be surveyed for the development of colon cancer, and they are predisposed to other malignancies, as well. LCCSCTs do not need to be removed, as they are typically benign, but gynecomastia in boys may be surgically treated (44, 45). Mild gynecomastia may successfully respond to treatment with aromatase inhibitors (45). Patients with PJS typically do well, as long as they are enrolled in regular clinical. Significant morbidity is caused by the development of polyps and the risk for colon and other malignancies.

COWDEN DISEASE

Cowden Disease (CD) is associated with hamartomas and tumors of ecto-, meso- and endodermal origin affecting multiple organs (46–48). Thyroid and breast masses, hamartomatous polyps, and mucocutaneous lesions (e.g., oral papillomatosis, acral keratosis,

and multiple fibromas) occur consistently in this syndrome, which is also associated with anomalies of the skeletal and nervous systems (43). CD was first mapped to chromosome 10; mutations in the tumor-suppressor gene *PTEN* on 10q were found shortly after that (46). CD is allelic to Ruvalcaba–Myhre–Smith, Bannayan–Zonana, or Bannayan–Riley–Ruvalcaba syndrome, which is also associated with hamartomatous intestinal polyposis, lentiginosis of the genitalia and developmental defects (e.g., macrocephaly and eye and skeletal anomalies), and myopathy (46–48). Both syndromes are due to mutations of the *PTEN* gene on chromosome 10, although genetic heterogeneity may exist (49).

NEUROFIBROMATOSIS Type 1 (NF-1)

NF-1 affects about 1 in 4000 individuals worldwide. NF-1 is clinically characterized by multiple café-au-lait spots and associated cutaneous neurofibromas (50, 51). The National Institutes of Health Consensus Conference developed diagnostic criteria that require at least two of main clinical features in order to diagnose NF-1 (52). These features include the cutaneous findings of café-au-lait macules, neurofibromas, and axillary freckling (Figure 3), and optic gliomas, iris hamartomas, bony abnormalities and other tumors (53–55)). Patients with NF1 are at an approximately 2–4 fold higher risk of developing tumors than the general population with a risk of malignancy estimated at between 5 and 15 percent (50). The gastrointestinal tract may be involved in NF-1 and includes mucosal and myenteric nerve hyperplasia, gastrointestinal stromal tumors (GIST), carcinoids, pheochromocytomas, paragangliomas, as well as pancreatic neuroendocrine tumors (50, 53–55).

TUBEROUS SCLEROSIS

Tuberous sclerosis (TSC) is an autosomal dominant neurocutaneous disorder with an incidence of approximately 1 in 5,000 to 10,000 live births (56); approximately 70–80% of TSC patients represent sporadic cases (57). TSC is a multisystem disorder with involvement of the brain, eyes, skin, heart, lungs and kidneys with characteristic hamartomatous lesions (50, 57). The classic TSC triad, known as Vogt's triad, includes mental retardation, seizures, and facial angiofibromas; the diagnostic criteria for TSC include the presence of two major features, or one major and two minor features (57). TSC is associated with an increased risk of benign as well as malignant tumors, especially in the kidneys, brain, and soft tissues. The relative risk of malignancy in children with TSC is approximately 18-fold higher than the general population. Although neuroendocrine tumors have been reported in patients with TSC, they are not currently considered one of the major features TSC (58, 59). A number of case reports have documented endocrine tumors in patients with TSC, and a recent systematic review summarized the available articles on this association (50). Pituitary tumors have been reported in four patients with TSC, including adrenocorticotrophic hormone, growth hormone, and prolactin secreting tumors (50, 58, 59). Both parathyroid adenoma and parathyroid hyperplasia have been reported. Rarely, pancreatic endocrine tumors including gastrinoma and insulinomas have also been described in TSC; there is also a report of a pheochromocytoma and a carcinoid occurring together with TSC (50). Molecular testing is widely available for TSC today (50, 60) as well as therapeutic trials of using TSC molecular pathway inhibitors (61).

CONCLUSION

Hereditary disorders associated with endocrine tumors range from the classic MEN syndromes to the neurocutaneous and phacomatoses conditions. In each of these disorders, skin manifestations are essential in diagnosing the disorder.

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Figure 1.
Lichen amyloidosis in a patient with MEN2A

Figure 2.

A, B, C: Lip, oral mucosa, and peri-oral pigmentation in a patient with PJS; **D:** Other pigmented lesions, such as café-au-lait spots, are also frequent in patients with PJS; **E, F, G, H:** some times, pigmented spots and nevi are found in unusual spots in patients with PJS.

Figure 3.

A; Multiple neurofibromas and pigmented skin lesions, as well as skeletal deformities in a patient with NF-1; **B:** Axillary freckling in the same patient.