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Gastroenteropancreatic neuroendocrine (carcinoid) tumors in children

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ABSTRACT

Neuroendocrine tumors (NETs) (previously termed carcinoids) are slow-growing tumors of the neuroendocrine system. They can occur anywhere within the body but are most commonly found in the midgut. This review is therefore confined to a discussion of gastroenteropancreatic NETS (GEP-NETS). GEP-NETS may be asymptomatic and are found incidentally (eg, during appendicectomy) or can present with symptoms attributable to either the site of the primary tumor or the secretion of serotonin and other substances from metastatic carcinoid disease (carcinoid syndrome). Symptoms of carcinoid syndrome include facial flushing, diarrhea, wheezing, colicky abdominal pain, and edema. Surgical resection offers the only curative treatment for neuroendocrine tumors, although peptide hormone analogues can be used to control carcinoid symptoms. Guidelines exist to determine when further surgical resection is required when NETs (carcinoids) are found incidentally during appendicectomy. A multi-disciplinary approach is essential for the management of all children with these rare and challenging tumors.

Introduction

Neuroendocrine tumors (NETs) are slow-growing tumors that arise from cells within the neuroendocrine system. They are rare, with a reported overall incidence of 2–3 per 100,000 persons per year,[1] and the incidence seems to be increasing.[2–4] The incidence of NETs varies amongst different ethnic groups, with African-Americans having the highest reported incidence of 6.5 per 100,000 per year.[2] In children, NETs can occur anywhere within the body, including the lungs,[5] bronchial tree,[6] thymus,[7] testis,[8] and thyroid[5] but are most commonly found within the gastrointestinal tract and the pancreas (gastroenteropancreatic NETS or GEP-NETs). According to the Surveillance, Epidemiology, and End Results (SEER) Program in the United States[1,3] and the Norwegian Registry of Cancer (NRC),[2] GEP-NETS comprise over 50% of NETs in all patients, and up to 67% of all NETs in the United States in patients of Afro-Caribbean origin. This overview is confined to a discussion of GEP-NETs.

Terminology and classification

There has been considerable confusion over recent years with regards to the nomenclature and classification of NETs. Previously, NETs were referred to as "carcinoids," a term first introduced in 1907 by the German pathologist Siegfried Oberndorfer to describe "carcinoma-like" tumors that were benign in behavior but demonstrated the microscopic features of malignancy (karzinoide).[9]

However, once it was realised that all NETs can become fully malignant, the term "neuroendocrine tumors" was introduced to describe the common cell origin of these anatomically varied tumors. Unfortunately, the term carcinoid had become well established, and it is still often used interchangeably with the term NETs by many clinicians. In 2000, the World Health Organization (WHO) attempted to clarify the term carcinoid, maintaining it for certain benign NETs in certain locations.[10] Other groups (including many pediatric surgeons) confine the term carcinoid to well-differentiated NETs of the gastrointestinal tract. More recent guidelines on NETs, however, have called for the cessation of the term carcinoid tumor altogether and for NETs to be classified by anatomical location, clinical syndrome, and degree of tumor differentiation.[11,12] The term carcinoid would then be used solely in the context of the "carcinoid syndrome" (see later).

In 2010, an updated WHO Classification was introduced (WHO 2010)[13] with some fundamental differences from the WHO 2000 Classification.[10,11] The WHO 2010 classification takes into account the fact that all NETs can become malignant and classifies NETs according to grade and stage, and simply uses the terms neuroendocrine tumor and neuroendocrine carcinoma (Table 1).

Pathology

NETs are an example of a "small blue cell tumor." All NETs demonstrate positive reactions to markers of neuroendocrine

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Table 1
A comparison of the different WHO classifications for NETs and carcinoids. The WHO 2010 guideline takes into account the fact that all NETs have malignant potential and restricts the use of the term "carcinoid." More recent guidelines have called on the term "carcinoid" to be only used in the clinical context of "carcinoid syndrome." (Reproduced with permission from Kloppel.[12])

WHO 1980	WHO 2000	WHO 2010
I. Carcinoid	1. Well-differentiated endocrine tumor (WDET)	1. Neuroendocrine tumor (NET) G1 (carcinoid) G2
	2. Well-differentiated endocrine carcinoma (WDEC)	
	3. Poorly differentiated endocrine carcinoma/small cell carcinoma (PDEC)	2. Neuroendocrine carcinoma (NEC) G3 large cell or small cell type
	4. Mixed exocrine–endocrine carcinoma (MEEC)	3. Mixed adenoneuroendocrine carcinoma (MANEC)
II. Pseudotumor lesions	5. Tumor-like lesions (TLL)	4. Hyperplastic and preneoplastic lesions

tissue, including neuron-specific enolase, synaptophysin, and chromogranin.[14–16] GEP-NETs vary in other histological features according to their anatomical location. Midgut NETs are characterized by positive silver staining (argentaffin positive), whereas foregut and hindgut NETs are argentaffin negative. Under electron microscopy, some NETs are found to have numerous neurosecretory granules containing different substances including serotonin, histamine, corticotropin, dopamine, and kallikrein.[14,15] Indeed, NETs were previously referred to as APUDomas, because they often demonstrated amine precursor uptake and decarboxylation to produce active amines such as serotonin and catecholamines. Release of these substances (especially serotonin) into the systemic circulation is responsible for the clinical features of carcinoid syndrome (see later).

Previously, the embryological origin of NETs was believed to be from cells migrating in from the neural crest. However, this is no longer believed to be the case. Indeed, it is now postulated that the origin of NETs in the gut and pancreas is from pluripotent progenitor cells that develop a neuroendocrine phenotype.[12]

As stated above, both the 2000 and 2010 WHO 2010 classifications of NETs distinguish NETs based on their degree of differentiation.[10,13] The 2000 WHO system included 3 groups: well-differentiated neuroendocrine tumors, well-differentiated (low grade) neuroendocrine carcinomas, and poorly differentiated (high grade) neuroendocrine carcinomas.[10] The WHO 2010 Classification includes a three-tier tumor grading system that is based on mitotic count or Ki-67 index[17] (Ki-67 antigen is a nuclear protein expressed by proliferating cells). G1 is defined as a mitotic count of <2 mitoses per High Power Field (HPF) and/or Ki-67 index of $\leq 2\%$; G2 as a mitotic count of 2–20 mitoses/10 HPF and/or Ki-67 index of 3–20%; and G3 as a mitotic count of >20 mitoses/10 HPF and/or ki-67 index of $>20\%$[13]. Staging is done by either the WHO TNM system or the ENETS TNM system depending on the anatomical location.[18,19]

Etiology

The precise etiology of GEP-NETs is unclear. The majority are sporadic, but some are associated with specific inherited familial syndromes including multiple endocrine neoplasia (MEN) 1, MEN 2, von Hippel–Lindau disease, neurofibromatosis type 1, tuberous sclerosis, and Carney complex.[20,21]

In addition to the genetic mutations identified with the familial syndromes above, a number of novel genetic mutations have been identified in association with pancreatic NETs.[18] One in six well-differentiated pancreatic NETs have mutations in the mTOR pathway genes (including TSC2, PTEN, and PUK3CA).[19] In addition, about 40% of pancreatic NETs are associated with mutations in the ATRX and DAXX genes that are part of a recently discovered cancer pathway.[22] These genetic mutations are distinct from those previously identified in pancreatic adenocarcinoma.

Clinical presentation

Depending on whether they secrete serotonin and the other substances described above, GEP-NETs are classified clinically as being either functioning or non-functioning. Functioning GEP-NETs present with symptoms and signs specific to the substances they produce (eg, pancreatic insulinomas). The classic clinical presentation associated with functioning GEP-NETs, particularly those of the midgut, is termed carcinoid syndrome (see later). Non-functioning GEP-NETs on the other hand can be either asymptomatic and found incidentally (eg, during appendicectomy) or symptomatic due to local effects of the primary tumor. Both the local and systemic effects of GEP-NETs can vary according to the anatomical site of the tumor.

Carcinoid syndrome

The symptoms of carcinoid syndrome include facial flushing, diarrhea, wheezing, colicky abdominal pain, and edema. It occurs in up to 5% of all NETs and in about 20% of patients with well-differentiated GEP-NETs of the midgut. Carcinoid syndrome associated with midgut GEP-NETS usually occurs when the disease has metastasized to the liver, whereas NETs in other anatomical locations (eg, the lung) do not have to be metastasized in order to produce it. This is because serotonin released into the portal circulation is metabolized to inactive products within the liver, whereas NETs that secrete directly into the systemic circulation result in the full effects of the substance secreted. This also explains why GEP-NETs that have locally invaded the retroperitoneum can also result in the carcinoid syndrome, as in such situation the venous drainage bypasses the liver. Carcinoid syndrome is less frequently seen in patients with primary GEP-NETSs in other anatomical sites, and indeed rectal NETs are very rarely associated with the carcinoid syndrome.[11] The cluster of symptoms and signs of carcinoid syndrome described above can be accompanied by right upper quadrant pain resulting from the local pressure of the hepatic metastases.

"Carcinoid crisis" is an acute and severe form of carcinoid syndrome usually triggered by anesthetic induction or manual handling/manipulation of a functional NET tumor.[23] Carcinoid crisis is extremely rare in children.

Pancreatic NETs

Pancreatic NETs (PNETs—to be distinguished from the same acronym for primitive neuroectodermal tumors) represent about a third of all GEP-NETs. They are frequently multi-focal. The majority (up to 60%) of PNETs are non-functioning.[24] Non-functioning PNETs can be large, and they often present late. Indeed, about 50% of non-functioning PNETs have metastasized by the time of clinical presentation.[11] Symptoms may be due to the local effects of the pancreatic mass and/or the hepatic metastases.