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Pancreatic endocrine tumors

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Abstract
Pancreatic endocrine tumours are rare tumours, and arise from the types of pancreatic cells that produce hormones. These tumours may or may not secrete hormones themselves and may or may not be cancerous (malignant). Functioning tumours secrete a particular hormones which may cause various syndromes. The present article reviews the latest reports on the pancreatic endocrine tumours

Keywords: Endocrine tumor, pancreas, tumor, insulinomas, gastrinomas.

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Introduction
Pancreatic endocrine tumours are rare tumours [1], and may produce a variety of hormones including insulin, gastrin, glucagon, pancreatic polypeptide, vasoactive intestinal peptide and somatostatin.

The most common pancreatic endocrine tumours are insulinomas and gastrinomas, which are respectively found within the pancreas and the gastrinoma triangle formed by the junction of the cystic and common bile ducts superiorly, the junction of the second and third portions of the duodenum inferiorly, and the junction of the neck and body of the pancreas medially [2, 3].

The tumors may be functional or non-functional, and may be benign or malignant. Most of non-functional tumors are malignant.

Epidemiology
Duodenopancreatic neuroendocrine tumors are rare, although current epidemiological studies worldwide suggest an incidence rate increase. It was assessed the pathological incidence of duodenopancreatic neuroendocrine tumors for 18 years in The Netherlands. Standardized excerpts from pathological reports of all patients who had a diagnosis of duodenopancreatic neuroendocrine tumors from 1991 until 2009 were collected from the Pathologisch Anatomisch Landelijk Geautomatiseerd Archief and reviewed. This nationwide network and registry of histopathological and cytopathological data covers 100 percent of the pathological reports in The Netherlands. It was identified 905 patients with pancreatic (n=692) or duodenal (n=213) neuroendocrine tumors. Most of these patients (69 %) had a nonfunctional tumor. Functional tumors were diagnosed at a younger age compared with nonfunctional tumors. The mean annual incidence rates per 1,000,000 persons over 1991 to 2009 were 2.54 for pancreatic and 0.81 for duodenal neuroendocrine tumors. The highest incidence was found in patients 65 to 79 years of age. The incidence of nonfunctional neuroendocrine tumors had increased significantly for two decades [4].

Effects of Sex Steroids
The endocrine pancreas is central in the physiopathology of diabetes mellitus. Nutrients and hormones control endocrine pancreatic function and the secretion of insulin and other pancreatic islet hormones. Although the pancreas is not usually considered as a target of steroids, increasing evidence indicates that sex steroid hormones modify pancreatic islet function. The biological effects of steroid hormones are transduced by both, classical and non-classical steroid receptors that in turn produce slow genomic and rapid non-genomic responses. In a review, it was focused on the effects of sex steroid hormones on endocrine pancreatic function, with special emphasis in

animal studies [5].

Effects of Serotonin

To determine if serotonin production by pancreatic endocrine neoplasms is associated with the pancreatic duct stenosis seen in patients with stenosis that is out of proportion to the size of the tumors seen on computed tomographic images an institutional approval was obtained for a study. Informed consent was waived. Clinical and radiologic findings in six patients were reviewed. Gross and histologic findings in the resected pancreas were also assessed. Formalin-fixed paraffin-embedded tumor sections were immunolabeled with antibodies to serotonin. Tissue microarrays constructed from 47 pancreatic endocrine neoplasms from the institutional tissue bank served as controls. Histological and serotonin immunoreactivity findings were compared between the two groups. The Fisher exact test was used to compare serotonin immunoreactivity. Only one of the six study patients had a large dominant tumor (4 cm in the pancreatic head). All others were 2.5 cm or smaller. Four of the six pancreatic endocrine neoplasms with associated pancreatic duct stricture had prominent stromal fibrosis. Serotonin immunoreactivity was present in five (83 %) patients, and this labeling was strong and diffuse in the four patients with prominent fibrosis. By contrast, stromal fibrosis was minimal in the nonimmunoreactive case. Only three (6 %) of the 47 control pancreatic endocrine neoplasms were immunoreactive for serotonin. It was concluded that these data suggest that serotonin produced by pancreatic endocrine neoplasms may be associated with local fibrosis and stenosis of the pancreatic duct. Clinicians should be aware that small pancreatic endocrine neoplasms can produce pancreatic duct stenosis resulting in ductal dilatation and/or upstream pancreatic atrophy out of proportion to the size of the tumor [6].

Multiple Endocrine Neoplasias

It was presented an update on molecular and clinical genetics of solid tumors associated with the various multiple endocrine neoplasias (MEN) syndromes. MEN type 1 (MEN1) describes the association of pituitary, parathyroid, and pancreatic islet cell tumors with a variety of many other lesions. MEN type 2 (MEN2) conditions represent at least four different syndromes that associate pheochromocytoma with medullary thyroid carcinoma, hyperparathyroidism, and a number of other manifestations. Other pheochromocytoma-associated syndromes include von Hippel-Lindau disease; neurofibromatosis 1; the recently defined paraganglioma syndromes type 1, 3, and 4; Carney-Stratakis syndrome; and the Carney triad. Carney-Stratakis syndrome is characterized by the association of paragangliomas and familial gastrointestinal stromal tumors. In the Carney triad, patients can manifest gastrointestinal stromal tumors, lung chondroma, paraganglioma, adrenal adenoma and pheochromocytoma, esophageal leiomyoma, and other conditions. The Carney complex is yet another form of MEN that is characterized by skin tumors and pigmented lesions, myxomas, schwannomas, and various endocrine neoplasias [7].

To identify gene expression alterations associated with insulinoma formation and progression in 2 mouse models of multiple endocrine neoplasia type 1 mice were killed at 12 or 16 months, and pancreatic islets were isolated by enzymatic and physical disruption. Islets were separated by size representing control, normal, hyperplastic, and adenomous islets. RNA was isolated from these islets and profiled on Sentrix Mouse-6 Expression version 1 BeadChips. Array data were analyzed in GeneSpring. One hundred and one genes that were significantly altered in hyperplastic islets and insulinomas compared with normal islets were identified. Of these, 64 gene elements showed reduced messenger RNA levels and 37 gene elements had increased gene expression compared with control islets. Altered expression of 3 genes, namely, Gata6, Tspan8, and s100a8, was confirmed by quantitative reverse transcription-polymerase chain reaction, and aberrant levels of Tspan8 and Lmo2 protein measured by Western blot correlated with the changes in messenger RNA levels. It was concluded that these results suggest that alterations in gene expression of Gata6, Tspan8, S100a8, and Lmo2 may act via novel pathways that play functionally important roles in Men1-associated tumor progression [8].

Insulinoma

Insulinomas are rare tumors with an estimated incidence of one per 250,000 person-years. Most insulinomas are benign with less than 10 percent demonstrating malignant behavior, the vast majority of which occur in adults. A systemic review of the literature revealed only nine cases of malignant insulinomas occurring in children. Herein, it was presented a case of metastatic malignant insulinoma in a 12-year-old child. The occurrence of this diagnosis in a child, its unusual pattern of metastases and the challenging management of severe hypoglycemia make this case worth reporting [9].

Metastatic insulinomas may present with recurrent life-threatening hypoglycemia. Treatment of hypoglycemia in such patients is difficult and frequently fails to respond to numerous therapeutic agents, requiring continuous dextrose infusion. The authors present the experience with Yttirum-90 radioembolization in a patient with metastatic malignant insulinoma who failed to respond to distal pancreatectomy, systemic chemotherapy with capecitabine and everolimus and medical treatment with somatostatin analogues, diazoxide and corticosteroids. Treatment with repeated Y-90 radioembolization resulted in rapid resolution of hypoglycemic events, allowing discontinuation of dextrose infusion and hospital discharge. However, the effect of Y-90 administration seems to be transient and without evidence of tumor shrinkage in imaging studies [10].

Octreotide Long Acting Repeatable

Octreotide long acting repeatable (LAR) is commonly used

to control the symptoms of patients with functional neuroendocrine tumors. Unfortunately, most patients escape control over time and require higher LAR doses or more frequent rescue therapy to remain asymptomatic. Previous work has shown that body weight and monthly LAR dose will significantly affect circulating plasma octreotide levels in patients undergoing therapy. To determine if other parameters change circulating plasma octreotide levels, it was prospectively studied 82 patients undergoing long-term LAR therapy. Multivariate analysis demonstrated that the plasma octreotide levels decrease by approximately 3.4 percent for each unit of body mass index (BMI) increase, adjusting for sex and monthly LAR dose. Plasma octreotide levels for females were approximately 48 percent higher than those for males, adjusting for BMI and monthly LAR dose. Initial and subsequent octreotide LAR doses should take into consideration sex and BMI. Males are estimated to require 14 mg higher monthly LAR doses than females with the same BMI [11].

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