Abstract
Gastroenteropancreatic neuroendocrine tumors (GEP NET) represent a heterogenous group of neoplasms: carcinoids (serotoninomas) and gastroenteropancreatic (insulinomas, gastrinomas, VIPomas, glucagonomas, somatostatinomas) respectively, unified by their origin (neuroendocrine cells), histology and immunohistochemical profile. Unlike their frequency in adults, the rarity of these lesions in childhood makes difficult their early diagnosis. Many tumors can be asymptomatic or may show non-specific features, the diagnosis being nevertheless based on clinical signs, dosage of hormonal specific peptides, nuclear medicine imaging and pathology confirmation. Baseline tests should also include chromogranine A and sinaptophysine. Localising studies comprise CT, MRI, somatostatine receptor scintigraphy and ultrasonography completed by endoscopy. Surgery is the mainstay therapy of GEP NET, as a complete removal can potentially cure the disease; debulking and metastasis surgery, together with adjuvant medical therapy can alleviate some symptoms, sometimes for a long period. Survival is variable, depending on tumour’s type, stage, histology and also on the completeness of the treatment.

Keywords: gastroenteropancreatic neuroendocrine tumors, child, neoplasms.

INTRODUCTION
An important group of GEP NET is constituted by pancreatic and duodenal lesions characterized by secretion of active hormonal polypeptides, which can determine a clinical syndrome or not. Although some of these tumors can produce more hormonal peptides, only one of them is responsible for a symptomatic answer. Also, the PNET can be unsecretory or secretory, the last ones being functionally or non-functionally active. According to their frequency, these lesions are represented by insulinomas, gastrinomas (Zollinger-Ellison syndrome), VIPomas, glucagonomas and somatostatinomas, the existence of the last two being contested in childhood. [1]

INSULINOMA. Although rare (1 case/250,000/year), it is by far the most common PNET in children. In the sixth decade of the last century, statistics of Mayo Clinics made mention of 224 cases of insulinomas, in only 4.9% of the cases the lesions being mentioned in children. Farquhar described a symptom appearing in the first weeks of life. [2-6] The menin gene has been shown as involved in the pathogeny of insulinomas, but also of another TNEPs. Most of these tumors, originating from β islet cells, and situated in the body or tail of the pancreas, are round or ovoidal, firm, circumscribed and yellow-brown coloured, with an average Ø of 2-2.2 cm (bigger lesions are malignant). Microscopy revealed uniform small to intermediary sized cells, nests and trabecular growth pattern, hyperchromatic nuclei and scanty cytoplasm. Clinically, the patients present neuroglycopenic symptoms dominated by neuropsychological manifestations: loss of consciousness, lethargy, confusion, dizziness, reccurent convulsions and coma followed by amnesia. Other troubles related to the catecholamine response, such as palpitations, tachycardia, hypertension and also hunger, epigastric pain or vomiting, were commonly registered. Some of the children were obese. [4,7,8] However, Whipple’s triad – consisting of manifestations of hypoglycemia, low plasma glucose level and relief of symptoms with administration of glucose – remains fundamentally sound. Malignant cases have been
reported in children [9], as well as a case of insulinoma with onset of symptoms at the age of 12.5 years in a patient having suffered from recurrent hypoglycemic seizures and gained 54 kg in weight. [10] Childhood insulinoma should not be confused with pancreatic neoplasia or persistent hyperinsulinemic hypoglycemia of infancy (PHHII), with a higher incidence in Saudi children and Ashkenazi Jewish populations, a hyperfunction of the β islet cells with 2, focal or diffuse, forms. The onset is early (hours/days after birth), with persistent hypoglycemia and hyperinsulinism, sometimes leading to sudden death. Biologic assessment of the insulinoma documented fast glucose lowering < 40 mg/dL and high insulin levels > 6 µU/l and C-peptide > 0.6 µg/ml. The rise in serum-immunoreactive insulin in response to secretin is significantly slower and smaller than in normal persons. Even if most of insulinomas are localized in the pancreas, the conventional localization methods cannot establish the preoperative location of the tumors, because of their small size. At present, combination of gadolin MRI, 3-phase CT, octreotate- PET and especially intraoperative palpation with US may detect almost all lesions. [1] The initial treatment of insulinomas is dietary, involving the use of frequent snacks (carbohydrates included) to prevent hypoglycemia. Diazoxide suppresses insulin secretion and enhances glycogenolysis. Octreotide and lanreotide maintain insulinemia within reasonable limits. Systemic chemotherapy, including combination of streptozocin and doxorubicin associated with (chemo) embolisation, peptide receptor radionuclide therapy, radiofrequency ablation or cryotherapy, can result in temporary palliation of symptoms and tumor growth. [8, 11] Surgery represents the only radical method of treatment: enucleation or limited distal, central or even cephalic resection (eventually laparoscopically done) for assuring a stable healing. Total pancreatectomy is reserved for resectable malignant cases, however debulking reductive surgery is more frequently possible.

**GASTRINOMA (Zollinger-Ellison syndrome)** (ZES) is represented by non-β cells solitary or multiple tumors of the pancreas or duodenum, generating aggressive forms of peptic ulcer disease by their excessive gastrin secretion. The lesions can be sporadic or familial, associated with MEN 1 in 25%, and malignant in 30% of cases. [12-14] The overall incidence of ZES, occurring sporadically or in association with MEN 1, is of 0.1-3/10^6/year. Childhood gastrinoma accounts for about 2% of all ZES. Until the end of the XXth century, 60 childhood gastrinomas had been reported worldwide; in 2004, Gibril analyzed a series of 107 children with ZES associated with MEN 1. [15] The youngest patient reported with Zollinger-Ellison syndrome was a boy aged 7 years. The incidence of this disease in male children is 4 times higher than in female children, in contrast with adults, in which a slight male predominance is noted. [16] Two-thirds of these tumors are situated in the “gastrinoma triangle” bounded by the junction between the cystic duct and the common bile duct, the junction between the second and the third part of the duodenum and the junction between the head and neck of the pancreas. Grossly, ZES are usually solid, firm, well-circumscribed but not incapsulated, and pale or yellow-brown in colour. When associated with MEN 1, they may be single or multiple, and may range from 1-3 cm Ø. Microscopically, these tumors are associated to children with neoplasia and show a compact pattern of monotonous sheets of small round cells with an uniform nucleus and cytoplasm and lack of mitoses. The presence of multiple ulcerous lesions with uncommon location and size (the second or third part of the duodenum, jejunum or larger than 2 cm), refractory to therapy and propensity to complications is significant. ZES symptomatology is related mainly to the excessive gastrin secretion rather than to tumor’s mass effects. Acid hyperproduction determines similar features with those of peptic ulcer and GERD, *i.e.* epigastric pain, pyrosis, dysphagia and diarrhea/steatorrhea, malabsorption (the last two consecutive cases, to the lesions of bowel mucosa, as well), together with upper and lower digestive hemorrhages, perforations, etc. In addition, family antecedents of endocrinopathies, and coexistence with MEN 1 and hypercalcemia are mentioned. [14,17] Despite the dramatically mentioned events, the diagnosis can be delayed for a number of years. Laboratory tests: elevated fasting level of gastrin > 300 pg/ml in association with an elevated basal
acid output > 15mEq/h are patognomonic for the diagnosis of gastrinoma, as also confirmed by the provocative secretin stimulation test. In the coexistence of MEN 1 somatostatin stimulation test and measurements of calcemia, PTH and prolactin are recommended. Conventional imagistic studies (US, CT, MRI) are of lesser utility in detecting small lesions, but somatostatin receptor scintigraphy is considered the imaging test of choice, localising both primary and metastatic PETs with 90% accuracy. Echoendoscopy and selective arteriography have proven their utility in detecting small tumors. Operative techniques such as palpation, duodenal transillumination and intraoperative ultrasonography can be used during laparotomy. Upper digestive endoscopy with multiple mucous biopsies is mandatory. (Fig. 1)

The drug treatment of ZES was revolutioned by the introduction of the new “potent” PPI (esomeprazole, lansoprazole, pantoprazole) and H2 blockers, so that all patients can experience control of acid hypersecretion. Somatostatin analogues, such as octreotide, known as decreasing gastrin and gastric acid secretion, can be used. However, all patients with sporadic gastrinoma should be candidates for surgical exploration. The goals of surgery are control of gastric acid hypersecretion and removal of malignant lesions with invasive and metastatic potential. The high accuracy of imaging studies, identification of the duodenal locus and an aggressive surgical approach with extensive lymphadenectomy and eventually hepatic metastasectomies increased the number of potentially curable operative explorations as a first line treatment. In cases of MEN 1-associated gastrinoma, the tumors are multiple and sometimes numerous, so that extirpation of the pancreatic or and duodenal tumor to reduce the malignant spread and eventually to increase survival by Whipple operation, partial duodenectomy or pancreatic preserving total duodenectomy, should be considered. Conservative surgery is performed for peptic ulcer disease complications. [8,14,18]

In inoperable cases, PPI and octreotide alone or associated with interferon represented a palliative solution. Chemotherapy with streptozocin, doxorubicin, and/or 5-fluorouracil may have important toxic effects. Patients with metastatic or inoperable tumors treated with 111In-DTPA octreotide, 90Y-DOTA⁰, Tyr³, or 177Lu-DOTA⁰, Tyr³ octreotate show symptomatic improvement and tumor regression. [19]

**VIPOMA** (VIP – vasoactive intestinal peptides) is a NET arising mainly from non-β cells in the body and tail of the pancreas but also in the mediastinum, retroperitoneum, colon and liver. In children, nevertheless, these tumors are most commonly found in the adrenals and sympathetic nodes originating from ganglioneuromas and ganglioblastomas. [20] Grosfield underlined that only two of his own 13 pediatric VIPomas were located in the pancreas. [21] Approximately 60% of vipomas are malignant and showed metastases at the time of diagnosis. The incidence in children is low: 0.05-0.2 new cases/10⁶/year, the literature mentioning only 63 observations. [22] The mean age of manifestation is 2.5-4 years, the most precocious case being described at a two week-age. [23] The male/female ratio is 1/1.5. Benign lesions have less than 2 cm Ø, are incapsulated, nonadherent and easy enucleable, being composed of trabecularly disposed rounded cells with scanty cytoplasm, ovoid nuclei and few mitoses. Non-β cell hyperplasia is rarely mentioned in children. Malignant cases invade the adjacent structures and spread to nodes, liver and lungs.Vipomas insidiously debutes with episodic diarrhoea (10 stools/day), persistent for months or even years before the diagnosis is established, coexisting with abdominal colics, dehydration (WDHA-watery diarrhoea, hypokalemia and achlorhydria), growth.

![Fig. 1: 3 duodenal ulcers in a 17 year-old boy with gastrinoma (Vth Pediatrics Clinics collection)](image)
delay, colon distension, miastenia, HTA, ataxia, etc. [24] Numerous children are treated for cow milk allergy, giardiasis or celiac disease. Laboratory studies evidenced marked hypokalemia, metabolic acidosis, hyperglycemia and potential renal failure. VIP serum levels are significantly increased over normal values: 160-250 pmol/L given to 20-30 pmol/L. Contrary to adults, child’s VIPomas are extrapancreatic. Chest-X ray analyses sometimes evidence a mediastinal mass, and plain abdominal radiography shows calcifications. In most cases, US, cervical, mediastinal and abdominal CT scanning, MRI, 99mTc, 123I and VIP receptors’ scintigraphy, SPECT and angiography can identify the lesion. [1,20,25]

Surgery is the standard therapy of these tumors, curable in benign VIPomas and in 40% of the malignant cases. Enucleation, distal pancreaticoectomy or Whipple operation can be done and, when possible, exeresis of secondary node or liver deposits should be performed. In extensive tumors, cytoreductive debulking surgery completed by embolisation, radiofrequency and chemotherapy are indicated. The medical treatment includes chemotherapy alone or associated with surgery, at relative rates of success. Interferon is recommended for its symptomatic effects, limiting hormone secretion and inhibiting tumoral growth. Octreotid reduced hormonal-mediated complaints and somatostatin analogues have antidiarrhoeic action, normalizing the hydroelectrolytic equilibrium and the acid-basic balance. [26]

**CONCLUSIONS**

Accelerated progresses of the medical practice and research in the last decades significantly modified the traditional concepts and taxonomy of the uncommon anatomo-clinical entities constituting the group of GEP NET. Better knowledge of the etiopathogenic mechanisms includes genetic and molecular biology for conturing newer lesion and clinical aspects. The refinements of diagnosis, the monitoring methods and the possibilities of surgical and medical therapies permitted a more precocious approach in pediatric patients. The recent therapy with fetal pancreatic cells, as well as the identification of further molecular markers, pathogenic pathways and a treatment focused towards neoangiogenesis, proliferation and apoptosis will lead to a significant increase of cases with stable cure and prolonged survival.

**References**


