Physiology of the endocrine pancreas

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The endocrine cells of the pancreas are grouped in the islets of Langerhans, which constitute approximately 1–2% of the Theodor Kocher , 1841–1917, Professor of Surgery , Berne, Switzerland, awarded the Nobel Prize in Physiology or Medicine in 1909. Paul Langerhans , 1847–1888, Professor of Pathological Anatomy , Freiberg, Germany . - y . If - /uni2032 - mass of the pancreas (Figure 57.14). There are about 1 million islets in a healthy adult human pancreas and their combined weight is 1–1.5 /uni00A0 g. There are four main types of cell in the islets of Langerhans, which can be classified according to their secretions: 1 β cells producing insulin (65–80% of the islet cells); 2 α cells producing glucagon (15–20%); 3 δ cells producing somatostatin (3–10%); 4 pancreatic polypeptide (PP) cells containing polypeptide (1%).

Malignancy (%) <10 60–90 60–90 40–70 50–80

> 70 60–90 s syndrome 95 Unknown eleasing factor; VIP , vasoactive intestinal polypeptide. Figure 57.14 Immuno /f_l uorescent labelling of endocrine (insulin [green]) and exocrine (amylase [red]) pancreatic cells and the nuclear marker DAPI (4 ,6-diamidino-2-phenylindole; blue) (courtesy of Dr Esni, Department of Surgery, University of Pittsburgh, USA).

Definition This is an insulin-producing tumour of the pancreas. Incidence These are rare tumours with an incidence of four (1–32) per million. Insulinomas have been diagnosed in all age groups, with the highest incidence found in the fourth to the sixth decades. Women seem to be slightly more frequently a ff ected. Pathology (including prognosis) The aetiology of insulinomas is unknown. They are equally scattered throughout the pancreas. Tumours are graded according to World Health Organization (WHO) NET criteria (Table 57.5). Tumours <2 /uni00A0 cm in diameter without signs of invasion are considered benign. More than 90% are both benign and solitary . Approximately 10% are associated with MEN /uni00A0 1. Clinical presentation Patients typically develop sporadic symptoms of neuroglycope nia. Classically these manifest while fasting or during exercise, but some (18%) may develop symptoms postprandially and these may be the only symptoms. Some patients develop loss of consciousness and coma. The release of catecholamines produces symptoms such as sw eating, weakness, hunger, tremor, nausea, anxiety and palpitations. The diagnosis can be elusive owing to its rarity and it is not uncommon for patients to have been investigated for epilepsy (fitting, loss of consciousness) or drug abuse (altered mental state) before the correct diagnosis is established. It is typical that patients will have put on weight

prior to presentation (learning to eat to survive). Diagnosis (with differential) The cornerstone of diagnosis remains Whipple's triad: /uni25CF symptoms induced by fasting; /uni25CF hypoglycaemia at the time of symptoms; /uni25CF symptoms relieved by administration of glucose. The key test is a 72-hour fast looking for documented endogenous hyperinsulinism in association with symptoms and George Hoyt Whipple , 1878–1976, Professor of Pathology , University of Rochester, Rochester, NY , USA, described this disease in 1907. He shared the 1934 Nobel Prize in Physiology or Medicine with George Richards Minot and William Parry Murphy 'for their discoveries concerning liver therapy against anaemias'. and high C-peptide. If the test is negative and the suspicion of insulinoma is high, a prolonged oral g lucose tolerance test is done. Di ff erential diagnoses include postprandial syndrome after gastrointestinal surgery , dumping syndr ome, factitious hypo - glycaemia, ethanol ingestion and pancreatic transplanta tion. Nesidioblastosis is a rare disorder, mainly encountered in children, that is characterised by replacement of normal pan - creatic islets b y di ff use hyperplasia of islet cells. After a positive fast test, a CT or MRI is performed. In only a small percentage (<5–10%) insulinomas are elusive on cross-sectional imaging. In such a situation endoscopic ultra - sonography (EUS) is undertaken with a positive detection rate in excess of 90%. Visceral angiograph y with arterial stimu - lation venous sampling is reserved for negative EUS studies or when mor e than one lesion has been identified. Another prom - ising method is scintigraphy with radiolabelled glucagon-like peptide 1, which is often overexpressed by insulinomas. Ho wever, this is not universally a vailable. MEN /uni00A0 1 should be considered in younger patients and those with multiple lesions. Chromogranin A is not a useful test for this tumour. Treatment (medical and surgical) Patients require treatment because of their symptoms. Surgery Most insulinomas are small, sporadic and solitary . In most cases enucleation is possible. Contraindications to enucleation are close proximity to the main pancreatic duct and larger tumours. In most cases a laparoscopic approach is recom - mended for localised tumours and this achieves a high success rate (98–100%). Postoperatively , blood sugar levels begin to rise in most patients within the first few hour s after removal of the tumour. To preserve pancreatic function and reduce the - risk of iatrogenic diabetes mellitus, patients in whom tumour localisation is not successful at operation should not undergo blind resection. For patients with MEN /uni00A0 1, tumours may be multifocal. The classical approach was to enucleate tumours in the 'right' pancreas (dictated by the portal vein) and perform a distal pancreatectomy owing to the high number of non-functioning NETs associated with the mutation. Laparoscopic enucleation of localised tumours has become the procedure of choice. Medical All patients undergoing surgery should be treated with diazoxide, which suppresses insulin secretion by direct action on the β cells, and receive frequent small meals to avoid hypoglycaemia. Somatostatin analogue (SSA) therapy may also be useful. For patients with unresectable or metastatic disease, SSAs and everolimus are e ff ective in controlling hypoglycaemia. Other options include chemotherapy , peptide rece ptor radio - nuclide therapy (PRRT) and chemoembolisation.

TABLE 57.5 World Health Organization neuroendocrine tumour (NET) classi /f_i cation of tumour grades. Grade Mitoses/10 /uni00A0 HPFs Ki-67 index Grade 1 NET <2 <3 Grade 2 NET 2–20 3–20

> 20 20 Grade 3 NET (well differentiated with high proliferative index) NEC (poorly 20 20 differentiated NEC) HPF , high-power /f_i eld; NEC, neuroendocrine carcinoma.

Definition Zollinger–Ellison syndrome (ZES) is a condition that includes: (i) fulminating ulcer diathesis in the stomach, duodenum or atypical sites; (ii) recurrent ulceration despite ‘adequate’ therapy; and (iii) non- β islet cell tumours of the pancr (gastrinoma). Incidence This is a rare disease a ff ecting between 0.5 and 4 in a million. Approximately 0.1% of patients with duodenal ulcers have evidence of ZES. Up to 20–25% of ZES is associated with MEN. Pathology In sporadic disease the tumours are mostly located in the duodenum (60–80%) and are small (<5 /uni00A0 mm) and multiple. In MEN /uni00A0 1, all tumours are in the duodenum. The vast majority (approximately 90%) occur within the ‘gastrinoma triangle’, an area bounded by the junction of the neck and body of the pancreas medially , the junction of the second and third parts of the duodenum inferiorly and the junction of the cystic and common bile ducts superiorly (Figure 57.15). Tumours are graded according to WHO NET criteria (Table 57.5 general, the progression of gastrinomas is relatively slow with a 5-year survival rate of 65% and a 10-year survival rate of 51%. Patients with complete tumour resection have excellent 5- and 10-year survival rates (90–100%). Patients with pancre atic tumours have a worse prognosis than those with primary tumours in the duodenum. There is no established marker to predict the biological behaviour of gastrinoma. Clinical presentation Over 90% of patients with gastrinomas have peptic ulcer disease, often multiple or in unusual sites. Diarrhoea is another common symptom, caused by the large volume of gastric acid secretion. Abdominal pain from either peptic ulcer disease or gastro-oesophageal reflux disease remains the most common symptom, occurring in more than 75% of patients. Around 60–95% have a history of high alcohol use, which may be a risk factor. The majority of tumours have metastasised by the time of presentation. Diagnosis (with differential) The cornerstone of diagnosing ZES is an elevated fasting serum gastrin (FSG). If elevated, the gastric pH is measured. If the pH is <2 and the FSG is more than 10-fold elevated, the diagnosis is confirmed. If the FSG is less than 10-fold higher, a secretin provocation test should be performed. The diagnosis is becoming more di ffi cult because of unreliability of some commercial gastrin assays and the widespread use of proton pump inhibitors (PPIs), which not only increases the pH of the stomach but also leads to inappropriate elevation of FSG in Robert Milton Zollinger , 1903–1992, Professor of Surgery , The Ohio State University , Columbus, OH, USA. Edwin Homer Ellison , 1918–1970, Professor of Surgery , Marquette University , Milwaukee, WI, USA. Zollinger and Ellison described this condition in a joint paper in 1957 when they were both working at The Ohio State University . eas the presence of hypergastrinaemia when gastric acid secretion is present.). In Hypergastrinaemia is seen in atrophic gastritis, PPI therapy and Helicobacter pylori infections and so all conditions feature in the di ff erential diagnosis. Once a diagnosis is confirmed all patients are screened for MEN /uni00A0 1 (biochemical and genetic). - Localisation studies are then indicated as the tumours are often small and multiple. The majority of gastrinomas have 68 a high density of somatotropin receptors. Ga-labelled SSAs with PET-CT have been found to be sensitive and specific. If not available, somatostatin scintigraphy (SRS) and EUS should be done. Chromogranin A is an unreliable test for gastrinoma. Treatment Surgery All patients with sporadic gastrinoma without metastases should have a surgical operation by an experienced surgeon. At the time, the peritumoral lymph nodes should be sampled for histological assessment. In MEN /uni00A0 1/gastrinoma, surgery is not recommended for patients with tumours <2 /uni00A0 cm. Tumours >2 /uni00A0 cm are enucleated. Parathyroidectomy reduces gastric acid secretion. Medical PPI therapy is the management of choice. Even when patients undergo a surgical cure, most (60%) require continued medical treatment. For patients with advanced locoregional disease or metastases, PPI remains the first-line treatment supplemented with SSA therapy . In refractory cases, locoregional ablative therapy (radiofrequency ablation or chemoembolisation) or PRRT may

be e ff ective.

Figure 57.15 The gastrinoma triangle.

Resectable • Clinical presentation No distant disease • Biology

- CgA and PP • Imaging
- CT/MRI
- EUS (with/without biopsy)
- SSR imaging Unresectable
- Octreoscan and/or
- Gallium PET-CT distant disease Figure 57.16 Algorithm for the investigation and management of non-functioning pancreatic neuroendocrine tumours. CgA, chromogranin A; CT, computed tomography; EUS, endoscopic ultrasonography; MRI, magnetic resonance imaging; NEC, neuroendocrine carcinoma; PET, positron emission tomography; PP , pancreatic polypeptide; SSA, somatostatin analogue; SSR, somatostatin scintigraphy; SSTR, somatostatin receptor.

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