Review

The management of insulinoma

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Background: Insulinomas are rare tumours. Their clinical presentation, localization techniques and operative management were reviewed.

Methods: An electronic search of the Medline, Embase and Cochrane databases was undertaken for articles published between January 1966 and June 2005 on the history, presentation, clinical evaluation, use of imaging techniques for tumour localization and operative management of insulinoma.

Results and conclusion: Most insulinomas are intrapancreatic, benign and solitary. Biochemical diagnosis is obtained during a supervised 72-h fast. Non-invasive preoperative imaging techniques to localize lesions continue to evolve. Intraoperative ultrasonography can be combined with other preoperative imaging modalities to improve tumour detection. Surgical resection is the treatment of choice. In the absence of preoperative localization and intraoperative detection of an insulinoma, blind pancreatic resection is not recommended.

Paper accepted 6 November 2005
Published online in Wiley InterScience (www.bjs.co.uk). DOI: 10.1002/bjs.5280

Introduction

Insulinomas are rare tumours. The incidence in individuals is 1–2 per million per year in the UK. Patients present with symptoms of hypoglycaemia secondary to insulin hypersecretion, or with non-specific, episodic symptoms that could be mistaken for a neuropsychiatric disorder. Even after biochemical confirmation, localization of an insulinoma can be challenging. This paper discusses the clinical presentation and diagnosis of insulinoma, with particular emphasis on localization techniques, and discusses the management of these elusive tumours.

Methods

An electronic search of the Medline, Embase and Cochrane databases was undertaken for articles published between January 1966 and June 2005, with emphasis on the history, presentation, clinical evaluation, preoperative and intraoperative localization techniques and operative management of insulinoma.

Historical perspective

Paul Langerhans first described pancreatic islets in 1869. In 1922, insulin was discovered by Banting and Best. Five years later, Wilder et al. reported an islet cell carcinoma in an orthopaedic surgeon suffering from hypoglycaemic symptoms. William Mayo performed an exploratory laparotomy on him and found a pancreatic tumour with multiple liver, lymph node and mesenteric metastases. An extract prepared from the tumour demonstrated insulin-like activity on injection into a rabbit. Roscoe Graham performed the first curative operation for benign insulinoma in 1929 in Toronto. Subsequently, Wermers reported disorders of one or more endocrine glands in five members of one family in 1954. This familial syndrome, once called Wermers syndrome, is now known as multiple endocrine neoplasia type 1 (MEN-1). Virtually all insulinomas are intrapancreatic in location. The median age at presentation is 47 (range 8–82) years, and there is a female preponderance (female to male ratio 1:4:1). Most are solitary lesions, but 10 per cent are multiple. The lesions are usually small with a diameter of less than 2 cm in 90 per cent, and less than 1.3 cm in 50 per cent of patients. Most insulinomas are benign; only 10 per cent have any evidence of malignancy. After successful surgical excision, the long-term survival is 88 per cent at 10 years with a higher risk of recurrence in patients with MEN-1.
Genetics

MEN-1 is an autosomal dominant familial cancer syndrome, characterized by tumours of the parathyroids, enteropancreatic endocrine tissues and the anterior pituitary gland. The syndrome results from inactivation of the menin gene, a tumour suppressor gene located on chromosome 11q13. A germline MEN-1 mutation underlies all or most cases of familial or sporadic MEN-1. The National Institutes of Health demonstrated germline MEN-1 mutations in 47 of 50 index cases of MEN-1 and in seven of eight patients with sporadic MEN-1. Importantly, a somatic MEN-1 mutation is the most common gene mutation in many sporadic endocrine tumours. Most insulinomas are sporadic in origin, with only 7.6 per cent associated with MEN-1. In MEN-1 the mean age at presentation is younger, at 25 years or less. Interestingly, a somatic MEN-1 mutation has been described in 17 per cent of sporadic insulinomas.

Clinical presentation

Patients with an insulinoma present with symptoms of hypoglycaemia secondary to excessive and uncontrolled secretion of insulin. Symptoms are often non-specific, episodic, vary among individuals and can differ from time to time in the same individual. Hypoglycaemic symptoms can be divided into two categories: neuroglycopenic and neurogenic symptoms. Neuroglycopenic symptoms are due to central nervous system neuronal glucose deprivation. They include behavioural changes, confusion, visual changes, fatigue, seizures and loss of consciousness. If hypoglycaemia is severe and prolonged, death may result. Neurogenic symptoms are due to autonomic nervous system discharge caused by hypoglycaemia. This results in cholinergic symptoms including hunger, sweating and parasthesia, and adrenergic symptoms including anxiety, tremor and palpitations. Cholinergic symptoms are mediated by acetylcholine released from sympathetic postganglionic neurones. Noradrenaline release from sympathetic postganglionic neurones, the adrenal medulla or both and adrenaline released from the adrenal medulla mediate adrenergic symptoms.

A shift in glycaemic thresholds for responses to low plasma glucose occurs in a patient with an insulinoma resulting in tolerance of abnormally low plasma glucose levels without symptoms. In addition to insulin, tumours can secrete other hormones, including serotonin, gastrin, glucagon, somatostatin, pancreatic polypeptide, corticotrophin and chorionic gonadotropin.

Classification of hypoglycaemia

Hypoglycaemia can result from deficient glucose production, excessive glucose use, excessive external glucose loss, or a combination of these. Hypoglycaemia is further classified as postabsorptive or postprandial (Table 1). Reproducible postabsorptive hypoglycaemia, commonly referred to as fasting hypoglycaemia, implies the presence of disease and requires further evaluation.

Hypoglycaemia due to excessive endogenous insulin secretion can be caused by a primary pancreatic β cell disorder including an insulinoma, β cell hyperplasia or nesidioblastosis, a β cell secretagogue including a sulphonylurea or a β cell-stimulating antibody, or an antibody to insulin. Non-β cell tumours causing postabsorptive hypoglycaemia include large intrathoracic, intra-abdominal or retroperitoneal tumours. Tumour types include slow-growing mesenchymal tumours such as fibrosarcoma, rhabdomyosarcoma, leiomyosarcoma and mesothelioma, which make up 50 per cent; 25 per cent are epithelial tumours, including adrenocortical carcinomas, hepatomas and carcinoid tumours, and various carcinomas, leukaemias and lymphomas cause the rest. Postprandial hypoglycaemia, commonly known as reactive or stimulatory hypoglycaemia, can be caused by congenital defects of enzymes of carbohydrate metabolism, gastric surgery or an idiopathic disorder.

Table 1 Causes of hypoglycaemia

<table>
<thead>
<tr>
<th>Postabsorptive hypoglycaemia</th>
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<tbody>
<tr>
<td>Drugs</td>
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<tr>
<td>Insulin</td>
<td>Pancreatic β cell disorder</td>
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<tr>
<td>Sulphonylureas</td>
<td>β cell secretagogue Autoimmune</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
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<tr>
<td>Pentamidine, quinine, propranolol, haloperidol</td>
<td>Renal failure Congestive cardiac failure, shock Starvation</td>
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<td>Salicylates, sulphamides</td>
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<tr>
<td>Sepsis</td>
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<tr>
<td>Hepatic failure, cirrhosis</td>
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<tr>
<td>Renal failure</td>
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<tr>
<td>Starvation</td>
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<td>Starvation</td>
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<td>Hormone deficiencies</td>
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<td>Hypopituitarism</td>
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<td>Addison’s disease</td>
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<tr>
<td>Non-β cell tumours</td>
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<tr>
<td>Endogenous hyperinsulinaemia</td>
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<tr>
<td>Congenital deficiencies of enzymes of carbohydrate metabolism</td>
<td>Glycogen storage diseases Galactosaemia Hereditary fructose intolerance Following gastric resection Idiopathic</td>
</tr>
</tbody>
</table>
Clinical evaluation

Hypoglycaemic symptoms can be non-specific, so it is important to obtain a plasma glucose level during symptoms. A normal plasma glucose concentration obtained during symptoms rules out the possibility of an insulinoma. Whipple’s triad – hypoglycaemic symptoms in the presence of low plasma glucose with relief of symptoms on administration of glucose – suggests endogenous hyperinsulinaemia. In general, venous plasma glucose levels higher than 3.9 mmol/l after an overnight fast are normal, levels between 2.8 and 3.9 mmol/l suggest hypoglycaemia and lower than 2.8 mmol/l indicates hypoglycaemia. Glycolysis in vitro, otherwise known as pseudohypoglycaemia, can result in erroneously low measured glucose levels in the presence of leucocytosis, thrombocytosis or polycythaemia.

Therapeutically administered antidiabetic drugs, notably insulin and the sulphonylureas, are the most common cause of hypoglycaemia. Accidental, surreptitious or malicious administration of these drugs should be considered in any patient presenting with hypoglycaemia. Commercially sold insulin preparations contain no C-peptide, so undetectable plasma C-peptide in a patient with hypoglycaemia and raised insulin levels indicates an exogenous source of insulin. Sulphonylureas result in glucose, insulin and C-peptide patterns indistinguishable from those produced by a primary β-cell disorder, therefore the measurement of plasma sulphonylurea level is essential. Insulin receptor-stimulating antibodies can cause hypoglycaemia. In these patients, insulin levels are high, and plasma glucose and C-peptide levels are low. Antibodies directed to insulin produce hypoglycaemia during the transition period from the postprandial to postabsorptive state as insulin secreted in response to an earlier meal slowly dissociates from the antibodies. In these patients, total and free plasma insulin levels are inappropriately high, insulin secretion is appropriately suppressed, free plasma C-peptide levels and proinsulin levels are low, but total C-peptide and proinsulin levels are high because of cross reactivity with antibody-bound proinsulin with its C-peptide sequence.

In the case of an insulinoma, symptoms are typically evident in the morning after an overnight fast, and are often precipitated by exercise. Patients learn to avoid symptoms by eating frequent small meals and sugary snacks, with resultant weight gain. A supervised 72-h fast forms the basis for the diagnosis of endogenous hyperinsulinaemia. The critical pathophysiological feature is failure of insulin secretion to fall to very low rates during episodes of hypoglycaemia. After admission to hospital, intravenous access is established, and the patient is allowed to drink only water during the fast, and encouraged to exercise. A sample of blood is taken every 6 h or when the patient is symptomatic, for plasma glucose, insulin, C-peptide, sulphonylurea screen and β-hydroxybutyrate level. The fast is ended when the plasma glucose falls below 2.2 mmol/l in association with hypoglycaemic symptoms. The patient then receives 1 mg of intravenous glucagon, and plasma glucose is measured after 10, 20 and 30 min. From published reports, symptoms develop in 35 per cent of patients within 12 h, 75 per cent within 24 h, 92 per cent within 48 h and 99 per cent within 72 h.

The presence of hypoglycaemic symptoms with fulfilment of the following criteria is diagnostic for insulinoma: blood glucose level 2.5 mmol/l or lower, insulin level 6 μunits/ml or higher, C-peptide level 0.2 mmol/l or higher, and a negative sulphonylurea screen (Table 2). In patients who develop severe symptoms and signs during the 72-h fast before the diagnostic criteria are fulfilled, additional evidence in support of the diagnosis can be helpful (Table 2). A rise in peak plasma glucose concentration by 1.4 mmol/l or more within 30 min in response to 1 mg of intravenous glucagon at the end of a prolonged fast indicates hyperinsulinaemia. Plasma β-hydroxybutyrate levels are low in patients with insulinoma because of the antiketogenic effect of insulin. Glucagon given at the end of a fast results in counteraction of the glycogenic and antglycogenic effect of insulin. If glycated haemoglobin levels are lower than 4 per cent (normal 4–7 per cent), this also supports the presence of an insulinoma. Other tests include C-peptide suppression and tolbutamide tests, which are not commonly used.

Non-islet cell tumours can cause postabsorptive hypoglycaemia. The pathophysiology includes high rates of glucose utilization and ectopic insulin secretion. Plasma insulin, proinsulin and C-peptide levels are appropriately suppressed during hypoglycaemic episodes in the vast majority. An incompletely processed form of insulin-like growth factor II (big IGF-II) is overproduced, which cannot complex normally with circulating binding protein, resulting in raised free IGF-II and pro-IGF-II levels. Growth hormone secretion is suppressed, IGF-I levels are low and the ratio of IGF-II to IGF-I is raised.

Table 2 Diagnostic criteria for insulinoma after a 72-h fast

<table>
<thead>
<tr>
<th>Factor</th>
<th>Concentration</th>
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<tbody>
<tr>
<td>Plasma glucose</td>
<td>≤ 2.5 mmol/l</td>
</tr>
<tr>
<td>Plasma insulin</td>
<td>≥ 6 μunits/ml (43 pmol/l)</td>
</tr>
<tr>
<td>Plasma C-peptide</td>
<td>≥ 0.2 mmol/l</td>
</tr>
<tr>
<td>Plasma proinsulin</td>
<td>≥ 0.5 mmol/l</td>
</tr>
<tr>
<td>Plasma sulphonylurea</td>
<td>Negative</td>
</tr>
<tr>
<td>Plasma β-hydroxybutyrate</td>
<td>&lt; 2.7 mmol/l</td>
</tr>
<tr>
<td>Change in glucose with 1 mg glucagon</td>
<td>≥ 25 mg/dl at 30 min</td>
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Localization techniques

A number of techniques are available to localize a suspected insulinoma, including transabdominal ultrasonography, abdominal computed tomography (CT), magnetic resonance imaging, arteriography, endoscopic ultrasonography (EUS), transhepatic portal venous sampling, selective arterial calcium stimulation with hepatic venous sampling, 111In-labelled octreotide scan with single-photon emission CT, positron emission tomography, intraoperative ultrasonography and intraoperative palpation. In choosing the localization technique, specific tumour characteristics need to be considered. It is important to remember that most tumours are intrapancreatic, 80–90 per cent are solitary, 80 per cent are less than 2 cm in diameter and that they are distributed equally within the head, body and tail of the pancreas. Multiple tumours are found in only 8 per cent of patients associated with MEN-1, and 2 per cent of patients have diffuse islet cell hyperplasia, microadenomatosis, or adult neoplasia.

The sensitivity of transabdominal ultrasonography in the localization of pancreatic insulinomas ranges from 9 to 64 per cent. EUS has been used to improve accuracy in recent years. Sensitivities of up to 94 per cent (range 57–94 per cent) are reported. Transabdominal ultrasonography with frequency probes of 7.5–12 MHz allows higher image resolution. The EUS appearances of insulinoma are characteristic and include homogeneous hypoechoic, rounded lesions with distinct margins.

The availability of linear and curvilinear array EUS has broaden its applicability, with the ability to perform fine-needle aspiration cytology of suspicious lesions, contrast-enhanced EUS using Levovist and preoperative marking of lesions to facilitate surgical excision. Colour-coded Doppler transabdominal ultrasonography allows imaging of adjacent vessels. However, limitations of EUS are poor identification of pedunculated or adjacent lesions and weak differentiation of larger homogeneous tumours from surrounding parenchyma. Detection rates of 83–100 per cent of head and body lesions are reported compared with 37–60 per cent for pancreatic tail lesions.

Arteriography was considered the ‘gold standard’ for insulinoma localization. However, improved non-invasive imaging modalities, combined with reported sensitivities of 29–64 per cent, have decreased its use. A tumour blush is seen in only 50–55 per cent of patients. However, Geoghegan et al. correctly identified all solitary insulinomas in their series using magnification, subtraction films, superselective arterial catheterization and oblique views.

Transhepatic portal venous sampling and selective arterial calcium stimulation with hepatic venous sampling have been proposed as the most sensitive preoperative localization techniques by some authors. Transhepatic portal venous sampling can be used to identify the site of maximal insulin secretion. The technique involves transcutaneous, transhepatic needle puncture of the portal vein, with sequential placement of a sampling catheter into the splenic, superior mesenteric and portal veins. Numerous samples are taken to determine the site of raised insulin production. Selective arterial calcium stimulation with hepatic venous sampling is based on the fact that calcium is a potent secretagogue for abnormal β cells. It is a more sensitive and specific provocative test, and has largely replaced transhepatic portal venous sampling.

An arterial catheter is placed through the femoral artery into the coeliac axis for subselective arteriography. A separate femoral venous catheter is directed into the right hepatic vein. An angiogram is performed followed by selective cannulation of the splenic, superior mesenteric and gastroduodenal arteries. In general, the pancreatic body and tail are supplied by the splenic artery, the head by the gastroduodenal artery and the uncinate process by branches of the superior mesenteric artery, although there is considerable overlap. Calcium gluconate (5 ml bolus of 0.025 mEq/kg) in saline is injected locally into the gastroduodenal, superior mesenteric and splenic arteries. Samples (5 ml of blood) are taken from the right hepatic vein before and at 30, 60 and 120 s postinjection for insulin measurement. A twofold increase in insulin in the 30- or 60-s sample, or in both, confirms the diagnosis. This technique has a reported sensitivity of over 90 (range 87.5–100) per cent in the accurate localization of pancreatic insulinomas. The sensitivity is further increased by using selective arterial calcium stimulation with hepatic venous sampling combined with intraoperative ultrasonography. Although selective arterial calcium stimulation with hepatic venous sampling has a high detection rate, it is not used routinely in most centres as it is invasive, technically demanding and expensive. It may be appropriate when an insulinoma is strongly suspected but all non-invasive imaging tests are negative.

The advent of helical CT scanning has improved the detection of insulinomas compared with conventional CT. Gouya et al. examined the sensitivity of abdominal CT in the detection of insulinoma in 32 patients between 1987 and 2000. Diagnostic sensitivity was 94 per cent for dual-phase thin-section multidetector CT, 57 per cent for dual-phase multidetector CT without thin
sections and 29 per cent for sequential CT. The combination of biphasic thin-section helical CT and EUS resulted in an overall diagnostic sensitivity of 100 per cent. Early arterial phase imaging should be performed to enhance detection (Fig. 1). However, false-negative results can occur with pedunculated, non-hyperattenuating lesions, or where the tumour lies adjacent to major vessels. Recent advances in magnetic resonance imaging enable localization of small pancreatic insulinomas (Fig. 2). Optimal detection is achieved with fast spin-echo, fat saturation and dynamic contrast-enhanced techniques with mangafodipir. Other potentially effective new imaging techniques include \[^{11}\text{C}]\text{5-hydroxytryptophan}\) and \[^{18}\text{F}\]\text{labelled dihydroxyphenylalanine positron emission tomography scanning}\.

Somatostatin receptor scintigraphy plays a central role in locating and assessing primary gastroenteropancreatic neuroendocrine tumours. However, insulinomas have a low density of somatostatin receptors, and express the somatostatin subtype-2 cell surface receptor in only 50 per cent of tumours. Consequently, somatostatin receptor scintigraphy has a limited role in the evaluation of primary insulinomas. Evolving techniques include peptide receptor scintigraphy combined with anatomic imaging methods such as CT or positron emission tomography. In tumours that express somatostatin receptor, this can be determined along with detailed axial imaging. This technique has a role in tumour localization, and also for follow-up after treatment with peptide receptor radionuclide therapy.

Intraoperative imaging with intraoperative and intraduct ultrasonography can further enhance tumour detection rates. Intraoperative ultrasonography is done with a high-resolution probe (7.5–10 MHz), allowing direct imaging of the pancreas without the interference of overlying gas or organs. Relevant operative anatomy can be examined to determine the optimal resection method with respect to proximity of the tumour to the main pancreatic duct, combined with colour flow Doppler assessment of adjacent major vessels (Fig. 3). Sensitivities of up to 95 per cent are reported in the detection of pancreatic insulinomas. Intraduct ultrasonography has been used to identify small islet cell tumours, and shows promise in differentiating benign from malignant causes of localized stenosis of the main pancreatic duct. It uses a frequency of 20 MHz and has a reported detection rate of over 90 per cent in the diagnosis of 1–3-mm diameter lesions. However, it is not widely available, requires specialist skills to perform and interpret, and will probably remain confined to selected centres.

**Operative management**

Surgical resection is the treatment of choice and offers the only chance of cure. Overall cure rates of 75–98 per cent are reported after surgery, with prognosis dependent on the stage at presentation and whether complete resection was achieved. Recent guidelines for the management of gastroenteropancreatic neuroendocrine tumours suggest that surgery should be confined to specialist hepatopancreaticobiliary units. The surgery may use laparoscopic
Management of insulinoma

Fig. 3 Intraoperative ultrasonography image demonstrating a solid lesion within the pancreatic parenchyma (arrow)

Fig. 4 Surgical resection of a well circumscribed insulinoma of the distal body of the pancreas

or open techniques, and includes enucleation, resection and/or metastatectomy. Enucleation is indicated for small, benign tumours at least 2–3 mm from the main pancreatic duct. Intraoperative ultrasonography and intraduct ultrasonography can be used to measure the distance between the tumour margin and the main pancreatic duct. Macroscopically, lesions appear reddish-brown in colour in contrast to the surrounding yellowish pancreatic parenchyma, and possess a pseudocapsule with a clear plane of dissection between the tumour and the surrounding soft pancreatic parenchyma. Recent guidelines suggest enucleation is enough if the lesion is clearly localized before surgery, near or at the pancreatic surface, and easily defined intraoperatively. Histological confirmation of complete excision and the benign nature of the insulinoma are essential.

Resection is indicated when the tumour abuts the pancreatic duct or major vessels, or where malignancy is suspected with a hard, infiltrating tumour and puckering of the surrounding soft tissue, distal dilatation of the pancreatic duct or lymph node involvement. Resection options include distal pancreatectomy, pylorus-preserving Whipple procedure, or mid-body pancreatectomy, depending on the site of the insulinoma. A classic Kausch–Whipple or a total pancreatectomy is rarely indicated but may be justified in some patients. A spleen-preserving distal pancreatectomy (Fig. 4) is the procedure of choice for benign or low-grade malignant distal pancreatic disease other than carcinoma. Patients who undergo distal pancreatectomy and splenectomy have significantly more postoperative complications, in particular infection, than patients who have a spleen-preserving procedure. To determine completeness of tumour excision, a perioperative insulin assay is valuable. Peripheral blood insulin levels are measured preoperatively, during surgery and 5 min after resection with an 8-min immunnochemiluminescent insulin assay. Unfortunately, this assay is not available in most centres.

With advances in laparoscopic techniques, both laparoscopic enucleation and resection of pancreatic insulinomas have been performed successfully. Insulinomas are ideally suited, as most are solitary and benign. A recently reported retrospective multicentre study conducted in 25 European surgical centres demonstrated the feasibility and safety of laparoscopic pancreatic resection in selected patients. The study included 22 patients with benign and three with malignant insulinoma, and a variety of procedures were used, including enucleation, distal splenopancreatectomy, distal pancreatectomy with splenic preservation and pancreatoduodenal resection. Enucleation or distal pancreatectomy was performed in 97% of patients. The overall laparoscopic conversion rate was 14% per cent, and there were no postoperative deaths. The rate of postoperative pancreas-related complications was 31 per cent, and 6 per cent needed surgical re-exploration. As suggested by other groups, the use of laparoscopic ultrasonography facilitated laparoscopic resection. Its role in the accurate localization of the lesion, detection of proximity to vessels and the main pancreatic duct, and determination of the surgical resection margin is often invaluable.

Intraoperative frozen section is not performed routinely in most centres. It can provide information regarding the
nature of the tissue, but is often non-diagnostic and cannot assess features of malignancy accurately. Completeness of excision is assessed by gross pathological appearance and should be confirmed by formal histological examination. Blind pancreatic resection should not be performed for occult insulinoma in the absence of preoperative and intraoperative detection in the pancreas. In these circumstances, the surgical procedure should be terminated and the patient referred to a specialist centre.

As insulinomas are small and the pancreatic head parenchyma is thick, most non-palpable tumours are in the pancreatic head. Intraoperative ultrasonography can play a critical role in the identification of non-palpable lesions. In a series by Norton, only 33 per cent of insulinomas in the pancreatic head were palpable. However, intraoperative ultrasonography correctly identified 100 per cent of them.

In 80 per cent of patients with MEN-1 who have endogenous hyperinsulinaemia, there are multiple pancreatic tumours. In these patients, an 80–85 per cent subtotal pancreatectomy to the level of the portal vein with enucleation of lesions in the head of the gland is recommended to reduce the risk of exocrine and endocrine insufficiency. After resection, the risk of recurrence is greater in patients with MEN-1 (21 per cent at 20 years) than those without MEN-1 (5 per cent at 10 years and 7 per cent at 20 years).

**Malignant insulinoma**

Malignant insulinomas invade locally into surrounding soft tissue or structures, and also spread by lymph node or liver metastases. The prognosis is determined by the stage of the disease. Malignant pancreatic tumours are usually single and are larger, measuring 4-7 (range 1–9) cm or more in diameter. The absence of hepatic metastases is a major predictor of survival at 3 years. For localized disease, formal pancreatic resection and lymphadenectomy is recommended. An aggressive approach is recommended in the presence of metastatic disease, with concurrent resection of the primary tumour and synchronous hepatic metastases. Palliative resection is indicated when preoperative evaluation shows that more than 90 per cent of the tumour can be removed, combined with adjunctive ablative techniques. It is also indicated for symptom relief when best medical management fails or in the setting of a life-threatening complication such as gastrointestinal haemorrhage, biliary or intestinal obstruction. Patients with liver metastases, those with limited metastases outside the liver, those whose primary tumour can be controlled and those who have a reasonable performance status are candidates for surgical resection. Improved outcome has been demonstrated in patients with metastatic islet cell cancers managed aggressively with debulking surgery; their overall, progression-free and symptom-free survival rates are 71 per cent (median 76 months), 5 per cent (median 21 months) and 24 per cent (median 26 months) at 5 years. Danforth et al. demonstrated a median disease-free survival after curative resection of 5 years, with a recurrence rate of 63 per cent. Palliative resection was associated with a median survival of 4 years, compared
with 11 months after biopsy of the tumour only. Survival rates of 29 per cent at 10 years after resection are reported. Conventional contraindications to surgical resection including nodal or distant metastases, or superior mesenteric vein invasion may need to be reconsidered in patients with advanced neuroendocrine tumours.

Adjunctive techniques include hepatic arterial embolization, chemoembolization, local destruction and systemic chemotherapy. First-line chemotherapy includes streptozocin-based combinations with 5-fluorouracil or doxorubicin. Others are intensified doses of 5-fluorouracil, dacarbazine and epirubicin. Total response rates of 20–35 per cent and symptomatic improvement in 50 per cent are reported, with duration of response of 20–24 months. Second-line agents include interferon-α and octreotide. Cisplatin and etoposide are reserved for rapidly dividing tumours. Selective hepatic artery embolization can help when systemic treatment fails, with response rates of 50–90 per cent, and a median duration of 10–15 months. Although symptomatic response rates of 40–90 per cent have been observed, a radiological response is seen in only 15–40 per cent. Transcatheter arterial chemoembolization, using doxorubicin and cisplatin-based regimens, is reported to be an effective symptomatic and antiproliferative treatment in patients with progressive tumours. Patients with a tumour burden under 50 per cent and high Lipiodol (over 50 per cent) uptake have a greater response to transcatheter arterial chemoembolization than those with higher tumour burden. In the former group, there was a trend towards longer survival, with 5-year survival after diagnosis of 48 per cent. Combination regimens of transcatheter arterial chemoembolization and systemic chemotherapy have resulted in higher response rates in some studies with improved survival. Palliative radiotherapy has a limited role. In patients with somatostatin receptor-positive tumours, the use of radioactive isotopes combined with somatostatin analogues is well described: 111In-labelled diethylenetriamine penta-acetate (DTPA) octreotide and 90Y-labelled tetra-azacyclododecane tetra-acetate (DOTA) octreotide. Newer agents such as radiolabelled arginine-glycine-aspartate-DTPA-Tyr3 and 177Lu-labelled DOTA-Tyr3 octreotate have recently been reported. Local ablation techniques for liver metastases include alcohol injection, cryotherapy and radiofrequency ablation.

Medical management

Medical management of insulinoma is generally restricted to patients with unresectable metastatic disease, high-risk candidates for surgery, those not suitable for resection or in those who have undergone an unsuccessful operation with persistent symptoms. Options include dietary management, diazoxide, calcium channel blockers and somatostatin analogues. Patients are advised to avoid prolonged fasting and to take frequent meals and snacks, including complex carbohydrates. Diazoxide is an antihypertensive drug with hyperglycaemic effects. It acts directly on β cells suppressing insulin secretion, and enhances glycogenolysis. The recommended daily dose is 200–600 mg orally. Good symptom control is achieved in about 50 per cent of patients. However, significant side-effects of oedema, weight gain, hirsutism and nausea are common. The calcium channel blocker, verapamil, has also been used with some success. Octreotide, a synthetic somatostatin analogue results in only temporary and modest symptom relief. It can worsen hypoglycaemic symptoms owing to a greater suppressive effect on growth hormone and glucagon secretion than on insulin. A satisfactory response is reported in only 50 per cent of patients. Novel therapeutic approaches in the treatment of neuroendocrine tumours have been described, including inhibition of the epidermal growth factor receptor-sensitive tyrosine kinase by gefitinib.

Conclusion

Insulinomas are uncommon tumours. Most are intrapancreatic, benign and solitary. Non-invasive preoperative imaging to localize the lesion continues to evolve. Recent guidelines for the management of gastroenteropancreatic neuroendocrine tumours recommended a multimodal approach to detect primary tumours, which may include CT, somatostatin receptor scintigraphy, EUS, and in some centres selective arterial calcium stimulation with hepatic venous sampling. A biochemical diagnosis obtained during a supervised 72-h fast followed by high-quality dual-phase thin-section multidetector CT of the pancreas confirms the diagnosis and localizes the insulinoma in most patients. Further evaluation by EUS is valuable for insulinomas in the proximal pancreas. Other imaging methods may be reserved for patients with negative CT. Preoperative imaging combined with intraoperative ultrasoundography should enable accurate tumour localization in more than 95 per cent of patients, and blind pancreatic resection in the absence of tumour detection is not recommended. Laparoscopic enucleation is increasingly performed, and leads to long-term cure if the tumour is benign. Aggressive debulking surgery may benefit patients with metastatic insulinoma, particularly if they are young and fit for surgery.
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