In a small number of cases, insulinoma may occur within a syndrome of hereditary predisposition to pancreatic endocrine tumour. This mainly involves type-1 multiple endocrine neoplasia or Wermer syndrome (MEN1) since pancreatic tumours associated with Von Hippel-Lindau syndrome (VHL) and Bourneville’s tuberous sclerosis (BTS) are generally non-functional [1–5].

Such insulinoma of genetic aetiology shows clinical and evolution-related particularities as compared to sporadic insulinoma that should be taken account of in strategy treatment.

1. Guidelines

- serum phospho-calcium assessment should be performed in all cases of insulinoma to screen for primary asymptomatic hyperparathyroidism, which has a prevalence of nearly 90% in MEN1 at 50 years of age;
- genetic predisposition syndrome should be screened for in case of:
  - familial history of MEN1, VHL or BTS,
  - one or more associated conditions typical of MEN1, VHL or BTS,
  - patient under 40 years of age,
- multiple insulinomas or associated functional or non-functional pancreaticoduodenal endocrine tumours,
- recurrence of insulinoma despite surgery;
- in case of MEN1 associated with insulinoma, complete assessment to explore for other locations is mandatory;
- as in sporadic insulinoma, the only curative attitude in insulinoma of genetic aetiology is surgical resection;
- the surgical attitude should take account of multifocal status, based on preoperative imaging comprising CT or MRI plus endoscopic ultrasound. Peroperative ultrasound may be useful;
- the most effective procedure in MEN1 is caudal pancreatectomy associated to enucleation of cephalic lesions;
- medical treatment may be suggested to prepare for surgery in highly symptomatic forms or in case of recurrence or of malignancy. Indications and modalities are as in sporadic insulinoma;
- as onset of insulinoma is early in MEN1, screening of subjects with genetic predisposition should be early.

2. Rationale

2.1. Specificities of insulinoma associated with genetic predisposition

2.1.1. MEN1 [1–4]

The rate of insulinoma in MEN1 is 10–20%. Conversely, only 5% of insulinomas are associated with MEN1. The insulinoma may often reveal the pathology, the main characteristics of which are given in Box 1. Moderate or asymptomatic hyperparathyroidism, however, is pre-existent in most cases when screened for. Thus, a recent study [3] reported that insulinoma was the first manifestation of MEN1 in half the cases studied, while overlooked asymptomatic biological hyperparathyroidism was discovered in 90% of cases. Likewise, a recent retrospective study by the
primary hyperparathyroidism with multi-gland hyperplasia and/or adenoma and/or recurrence of primary hyperparathyroidism despite surgery;

- pancreaticoduodenal endocrine tumour, whether functional (gastrinoma, insulinoma, glucagonoma, other rare secretions) or not, multisecreting tumour with or without functional signs or hormonal expression on immunohistochemistry;

- Pituitary tumour, whether functional (GH, PRL, ACTH, etc.) or not, or multisecretion;

- functional or non-functional corticoadrenal tumour with or without hyperplasia;

- thymic or bronchial endocrine tumour;

- first degree relative presenting at least 1 of the cardinal lesions (listed above).

**Box 1: MEN1 diagnostic criteria.**

MEN1 is diagnosed for at least two of the following:

- Central Nervous System hemangioblastoma: 60–80%;
- retinal hemangioblastoma: 50–60%;
- renal cyst or tumour (renal clear-cell adenocarcinoma): 30–60%;
- cyst, serous cystadenoma or pancreatic endocrine tumour: 30–65%;
- pheochromocytoma: 11–19%;
- endolymphatic sac tumour: 2–10%.

Other lesions:

- cystadenoma of the ovary or large ligament;
- cystadenoma of the epididymis.

**Box 2: Clinical manifestations of VHL.**

Six major lesions:

- Central Nervous System hemangioblastoma: 60–80%;
- retinal hemangioblastoma: 50–60%;
- renal cyst or tumour (renal clear-cell adenocarcinoma): 30–60%;
- cyst, serous cystadenoma or pancreatic endocrine tumour: 30–65%;
- pheochromocytoma: 11–19%;
- endolymphatic sac tumour: 2–10%.

Other lesions:

- cystadenoma of the ovary or large ligament;
- cystadenoma of the epididymis.

**Box 3: Clinical manifestations of BTS.**

Multiple cutaneous-mucosal lesions: sebaceous adenoma, periungual fibroma, acrokeratosis, hypomelanitic macules, mucosal lesions

- Cerebral tuberosclerotic hamartomatosus sites
- Mental retardation and disorders
- Epilepsy
- Retinal phakoma
- Cardiac rhabdomyoma
- Liver, kidney, adrenal or pancreatic angiomyolipoma
- Pulmonary lymphangiomyomatosis
- Pancreaticoduodenal endocrine tumour

Malignancy is rare, at 8 to 10% depending on the series. The two main prognostic factors are tumour volume and liver metastasis.

2.1.2. VHL [1–5]

Box 2 presents the clinical manifestations of VHL. Pancreatic endocrine tumour develops in 8–17% of VHL patients, and is almost always non-functional and usually asymptomatic and multiple, although less diffuse than in MEN1. Metastasis is found in 10–20% of cases. Immunohistochemistry finds immunoreactivity to CgA, neuron-specific enolase, somatostatin, pancreatic polypeptide, gastrin, insulin and glucagon. Pancreatic endocrine tumour is the only manifestation of VHL in 7% of patients.

2.1.3. BTS [1,2]

Pancreaticoduodenal endocrine tumour is rare in BTS (Box 3). Localization is mainly pancreatic. It is usually non-functional, but may exceptionally take the form of gastrinoma or insulinoma.
2.2. Treatment strategy

Like in sporadic insulinoma, the only curative attitude in insulinoma of genetic aetiology is surgical. The surgical attitude, however, should take account of the characteristics of the insulinoma, which is usually multifocal, and will depend on the number and localization of lesions [13–16]. Rigorous preoperative imaging comprises CT or MRI plus endoscopic ultrasound. Peroperative ultrasound may be useful.

In MEN1, insulinoma is predominantly found in the body or tail of the pancreas. Enucleation of detectable lesions alone is associated with a high risk of recurrence of hyperinsulinism (40%). The most effective procedure consists in enucleation of cephalic lesions, associated in principle to caudal pancreatectomy sectioning the parenchyma facing the superior mesenteric vein [17,18]. Peroperative venous insulin assay may allow control of resolution [19,20]. Survivor after surgery adhering to guidelines is 97% at 5 years and 88% at 10 years. Recurrence is estimated at 21% by 20 years, compared to 7% in non-MEN1 patients [17,21].

Medical treatment may be suggested to prepare for surgery in highly symptomatic or malignant forms; indications and modalities are similar to sporadic insulinoma.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References