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Insulinoma of genetic aetiology☆,◊

Insulinome de cause génétique

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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 neoplasm 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 insulnomas 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 hyperthyroidism, 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

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☆ Hypoglycemia in non-diabetic patient.

◊ L'hypoglycémie chez le patient non diabétique.

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Box 1: MEN1 diagnostic criteria.

MEN1 is diagnosed for at least two of the following:

- 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).

Gubbio Conference, 1999

Groupe d'Étude des Tumeurs Endocrines (GTE) [6], including 86 consecutive insulinoma patients with MEN1, found that insulinoma was the first manifestation of the condition in 58% of cases, although one or more signs of MEN1 were present in two thirds of patients at diagnosis. Age at diagnosis is classically 30–35 years, that is 10 years less than in sporadic insulinoma, and expression may be very early [3,4,7]. In another GTE series of 124 patients under 20 years of age with symptomatic MEN1, insulinoma was the most frequent form of pancreatic tumour and was revelatory in 16 cases (11%); the youngest patient was 5 years old [8]. As onset of insulinoma is early in MEN1, screening of subjects with genetic predisposition should be early.

Insulinoma in MEN1 has the particularity of being multiple in 80–90% of cases. It is generally small (0.2–1.6 cm), making diagnosis difficult. It may be associated with other pancreaticoduodenal endocrine tumours, functional (gastrinoma, glucagonomas, VIPoma) or not, which may affect clinical symptomatology.

Clinical signs of hypoglycaemia are generally typical: fasting hypoglycaemia, hypoglycaemia not related with meals, associating signs of neuroglycopenia and of adrenergic response, although hypoglycaemia unrelated to meals cycles does not rule out diagnosis [9]. Fasting test, sometimes up to 72 hours, enables diagnosis.

The tumour or tumours may be difficult to localize. MRI and endoscopic ultrasound are more effective than CT [1,2,10].

Overall, 10-year survivor is 80–90%, well above that for other functional or non-functional pancreatic tumours [11,12].

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 cutaneo-mucosal lesions: sebaceous adenoma, periungual fibroma, acrochordon, hypomelanic macules, mucosal lesions
Cerebral tuberosclerotic hamartomatous sites
Mental retardation and disorders
Epilepsy
Retinal phakoma
Cardiac rhabdomyoma
Liver, kidney, adrenal or pancreatic angiomyolipoma
Pulmonary lymphangioleiomyomatosis
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 simular to sporadic insulinoma.

Disclosure of interest

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

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