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Diagnosis and Treatment of Insulinomas in the Adults

D. Vezzosi et al.*

*Department of Endocrinology, CHU Larrey, Toulouse
France*

1. Introduction

Insulinomas are rare endocrine tumours developed from pancreatic beta cells. Their incidence is about 1 in 250,000 patient-years (Cryer 2008) (0.396 per 100,000 person-years for two decades, 1967-1986) (Service et al. 1991). The median age at surgical diagnosis was found to be 47 years (8 to 82), 59% being female patients. In a series of 33 patients, the age at the time of diagnosis was 57 +/- 16 years (mean +/- SD) (range: 18-85 years) and 66% were female patients (Vezzosi et al. 2007). 90% of insulinomas are single, benign and sporadic tumours that are located in the pancreas. The diagnostic and therapeutic strategy of benign sporadic insulinomas has been now established by a recent expert consensus (Cryer et al. 2009). However, some issues remain unaddressed regarding the diagnosis and the treatment of insulinomas. More rarely, in about 10% of insulinoma patients, the insulinoma is part of MEN-1. Such patients often present with multiple insulinomas and other secreting or non-secreting endocrine tumours. Finally, a particular condition is malignant insulinoma, also found in about 10% of insulinoma patients. There are no recommendations regarding the particular conditions represented by insulinomas in MEN-1 and malignant insulinomas.

The aim of this chapter is to give an updated and detailed view of the medical management of adult patients with insulinoma regarding the diagnosis (diagnosis of hypoglycemia related to endogenous hyperinsulinism, differential diagnosis, topographic assessment) and the treatment (surgery, medical therapies), including the therapeutic strategy and the possibilities of long-term medical treatment in inoperable patients. The first part of the chapter will be focused on the most frequent case, i.e. single benign sporadic insulinoma. The remaining parts of the chapter will deal with specific issues and concerns regarding malignant insulinomas, insulinomas in genetic disorders, and the rare cases of nesidioblastosis in the adults.

*D. Vezzosi¹, A. Bennet¹, J.C. Maiza¹, A. Buffet¹, S. Grunenwald¹, J. Fauvel², F. Courbon³, P. Ota⁴, N. Carrere⁵ and Ph. Caron¹

¹Department of Endocrinology and Metabolic Diseases, CHU Larrey,

²Laboratory of Biochemistry, IFB, CHU Purpan,

³Department of Nuclear Medicine, CHU Rangueil,

⁴Department of Radiology, CHU Rangueil,

⁵Department of Surgery, CHU Purpan, Toulouse, France.

2. Single benign sporadic insulinomas

2.1 Diagnosis of hypoglycaemia related to endogenous hyperinsulinism

2.1.1 Clinical symptoms of insulinomas

The clinical symptoms of insulinomas are heterogeneous and may differ among the patients. There is no specific clinical symptom. Hypoglycaemia results in autonomic and neuroglycopenic symptoms. Autonomic symptoms comprise adrenergic symptoms, such as palpitations and tremor, and cholinergic symptoms, with sweating, hunger, sometimes paresthesias. Neuroglycopenic symptoms comprise severe weakness, and many psychiatric and neurological manifestations, the most commonly reported being behavioural changes, confusion, agitation or slow reaction patterns, blurred vision, and finally seizures, transient loss of consciousness or hypoglycaemic coma. Hypoglycaemic coma is typically sudden, with agitation, sometimes pyramidal signs, and hypothermia; it may be profound and prolonged and therefore may be a cause of neurologic and cognitive sequelae and may occasionally lead to brain death. The combination of autonomic and moderate neuroglycopenic symptoms strongly suggests the diagnosis of hypoglycaemia. However, in insulinoma patients, autonomic symptoms may often be lacking. Neuroglycopenic symptoms are more specific of hypoglycemia related to insulinoma, but may be mild, or more often misleading. Therefore measurement of plasma glucose concentrations should be recommended in all patients with such symptoms, either in a patient without any known neurological or psychiatric disorder, or in a patient in whom such disorder had been previously controlled. Hypoglycaemic spells typically occur suddenly after a period of fast, several hours after the last meal, or after physical exercise. Some of them have been reported to occur within the hours following a meal or without any relationship with meal time, so that symptoms occurring in non fasting patients cannot rule out the diagnosis of insulinoma. In a series of 214 insulinoma patients with a reliable clinical history, symptoms of hypoglycaemia were reported exclusively in the fasting state in 73%, postprandial state in 6%, and both fasting and postprandial state in 21% (Placzkowski et al. 2009). Weight gain is found only in 25% of patients.

Rapid (or rarely delayed) resolution of symptoms after glucose administration is part of Whipple's triad, which makes the diagnosis of hypoglycaemia when it has been assessed reliably; the triad comprises clinical symptoms of hypoglycaemia, the finding of a low plasma glucose concentration at the time of clinical symptoms, and subsiding of clinical symptoms after glucose administration.

In rare pregnant patients with insulinoma, symptoms may resemble those of emesis in early pregnancy and may subside in late pregnancy as a consequence of insulin resistance, then are unmasked after delivery (Diaz et al. 2008), as reported in a patient who presented with coma and clonic seizures 14 hours after delivery (Christiansen & Vestergaard 2008).

2.1.2 Biological diagnosis of insulinomas

Plasma glucose concentrations

Since the clinical symptoms lack diagnostic specificity, measurement of plasma concentration of glucose is mandatory (ideally at the time of occurrence of clinical symptoms) and must be performed in venous blood samples with a reliable laboratory method. In order to avoid pseudohypoglycaemia, i.e. a consequence of glucose metabolism by blood cells in the tube containing the blood sample, the blood sample should be collected in a tube with a glycolysis inhibitor (NaF). Glucose concentrations are measured using reference method with hexokinase.

The threshold to define hypoglycemia remains controversial. According to recent expert recommendations (Cryer et al. 2009) a 0.55 g/L threshold must be selected. However, the glycaemic threshold that can cause clinical symptoms is very different among individuals, and a plasma concentration of glucose below 0.7 g/L at the time of clinical symptoms is thought to be enough, if the other criteria of Whipple's triad are fulfilled, to warrant further investigation. A plasma glucose concentration above 0.7 g/L during a symptomatic episode indicates that those symptoms are not the result of hypoglycaemia.

Since even values below 0.55 g/L can be found in some healthy individuals, it is also recommended by the expert consensus that such levels be taken into account for further evaluation only in patients who had presented Whipple's triad. On the other hand, very rare insulinoma patients were found to be asymptomatic and did not fulfil Whipple's triad. Among our patients (Vezzosi et al. 2007), the diagnosis of insulinoma was made on the basis of repeated plasma glucose concentrations of 0.40-0.55 g/L after overnight fasts in one patient, though she never described any clinical symptom. In many insulinoma patients, the glycaemic threshold for clinical symptoms is shifted to very low glucose levels, so that they may be asymptomatic at the time of plasma glucose concentrations below 0.55 and even 0.45 g/L; most of these patients experienced some clinical symptoms suggestive of hypoglycaemia, but even if they present with fasting glucose levels below 0.55 g/L, Whipple's triad has not been assessed in most of them, and awaiting Whipple's triad to be fulfilled would make the diagnosis be delayed. The finding of a spontaneous plasma glucose concentration below 0.55 g/L is rare in normal subjects; during a 72-hour fast test, plasma glucose concentrations do not reach values below 0.45 g/L in most controls, and do not drop below 0.4 g/L in controls (Vezzosi et al. 2007). Therefore we think that patients with spontaneous plasma glucose concentrations below 0.55 g/L warrant further investigation, even when they do not fulfil all the criteria of Whipple's triad, and that such evaluation is mandatory in patients with plasma concentrations below 0.45 g/L, provided that plasma glucose concentration has been measured reliably in a venous sample.

Confirmation of hypoglycaemia in a venous sample is the first requirement for the biological diagnosis of insulinoma.

If a venous sample cannot be collected when hypoglycaemia occurs spontaneously, a 72 hour-fast test is to be performed.

A detailed protocol for the fast test has first been described by the Mayo Clinic group (Service 1995)(Service 1999) and more recently by an expert consensus (Cryer et al. 2009). The patient is allowed to drink calorie-free beverages. Samples are to be collected every 6 hours until the plasma glucose concentration is less than 0.6 g/L if the patient remains asymptomatic, then the frequency of sampling is increased (every 1 or 2 hours). Serum insulin, C-peptide, proinsulin and beta-hydroxy-butyrate are to be measured in all the samples taken at the time when plasma glucose concentration drops below 0.6 g/L. At the end of the fast test, a sample is collected to measure oral hypoglycaemic agents; a glucagon test (1.0 mg intravenously) has also been recommended. Insulin antibodies should also be measured.

The criteria used to decide to stop the fast test before 72 hours have been modified recently. According to previous recommendations (Service 1995), the fast test is to be stopped if the patient has symptomatic hypoglycaemia with a plasma glucose concentration of 0.45 g/L or less, or if the plasma glucose concentration drops below 0.4 g/L. According to the recent recommendations (Cryer et al. 2009) the fast test can be stopped: 1) when Whipple's triad is observed; 2) when plasma glucose concentrations drop below 0.55 g/L in a patient who had previously experienced Whipple's triad; 3) if plasma beta-hydroxy-butyrate levels rise above 2.7 mmol/L.

Awaiting that plasma glucose concentrations drop below 0.45 g/L in an asymptomatic patient to stop the fast test, instead of stopping the fast when plasma glucose is 0.46-0.54 g/L, leads to an improvement in diagnostic specificity regarding the diagnosis of a hypoglycaemic disorder. In our own data, out of 67 controls, 31 reached glucose plasma concentrations of 0.46-0.54 g/L during a 72-hour fast test, and only 4 reached values within the 0.40-0.45 g/L range (0.41-0.43 g/L) after 24 hours of fast. No control subject reached plasma glucose concentrations below 0.4 g/L. Among 55 patients who were diagnosed to have insulinoma in our institution between 1997 and 2010, and who underwent a fast test, only one patient reached a plasma glucose concentration below 0.55 g/L (0.53 g/L) without further decrease in glucose concentration, and all the other patients who had a positive fast test reached glucose concentrations below 0.45 g/L; the fast test was negative in one patient. In addition, using a 0.45 g/L glucose level threshold increases the diagnostic specificity of concomitant serum insulin, C-peptide and proinsulin levels for the diagnosis of insulinoma (see below). Therefore we think that if the patient remains asymptomatic, the fast test is to be prolonged at least until reaching plasma glucose concentrations below 0.45 g/L, the diagnostic specificity being about 100% if such levels are reached.

In most insulinoma patients such plasma glucose concentrations are reached within the first 48 hours of the test (Hirshberg et al. 2000; Vezzosi et al. 2007), though the 72 hour-fast test was reported to be necessary to provide a clear diagnostic conclusion in a few patients (Service 1999; Service & Natt 2000). Moreover, additional criteria for the diagnosis of insulinoma using proinsulin and beta-hydroxy-butyrate levels and plasma glucose response to intravenous glucagon were established during a 72-hour (not 48-hour) fast test for patients who did not reach plasma glucose concentrations below 0.45 or 0.55 g/L. Thus in most patients the test to be performed is the classical 72 hour-test. However, 48 hours of fast test are enough to provide diagnostic evidence in almost all insulinoma patients who have a positive fast test.

In the patients who experience symptoms of hypoglycemia only within the hours following a meal, a meal test is to be performed with serial measurement of plasma concentrations of glucose, insulin, C-peptide and proinsulin during the 5 hours following the ingestion of a standardized meal. A mixed meal similar to that which the patient reports to have caused the clinical symptoms is to be used, or a commercial formula mixed meal. Samples should be collected every 30 minutes and those collected for insulin, C-peptide and proinsulin measurement should be sent for analysis only if the sample has been taken at the time when plasma glucose concentration was found to be below 0.6 g/L. Measurement of oral hypoglycaemic agents and anti-insulin antibodies must also be performed if Whipple's triad is demonstrated (Cryer et al. 2009). Post-prandial hypoglycaemia without fasting hypoglycaemia is now known to occur in some insulinoma patients (6% according to Placzkowski et al. 2009) and in patients with noninsulinoma pancreatogenous hypoglycaemia (Service et al. 1999), a syndrome which is part of nesidioblastosis (see below). Others have reported false negative tests in insulinoma patients who are correctly diagnosed after a meal test or oral glucose tolerance test (Sjoberg & Kidd 1992) (Izumiyama et al. 2006; Kar et al. 2006). A mixed meal test was shown to be preferable to the oral glucose tolerance test (Hogan et al. 1983), so that only the meal test was recommended in the 2009 expert consensus.

The next requirement for the diagnosis of insulinoma is to provide evidence for inappropriate insulin secretion at the time of hypoglycaemia.

Criteria for inappropriate insulin secretion (hypoglycaemia related to endogenous hyperinsulinism)

According to the expert consensus, the diagnosis of hypoglycaemia related to endogenous hyperinsulinism can be made when serum insulin concentration is equal to or greater than 3 mIU/L, serum C-peptide concentration is equal to or greater than 0.6 ng/mL (0.2 nmol/L), and serum proinsulin concentration is equal to or greater than 5 pmol/L at the time of hypoglycaemia, with venous plasma glucose concentrations less than 0.55 g/L. During a fast test, beta-hydroxy-butyrate levels of 2.7 mmol/L or less and an increase in plasma glucose of at least 0.25 g/L after intravenous glucagon indicate mediation of hypoglycaemia by insulin.

Insulin

Serum insulin concentrations can be artifactually modified by haemolysis, heterophilic antibodies, and endogenous anti-insulin antibodies. Red cells contain an insulin-degrading enzyme which may lead to underestimation of the actual insulin concentrations on haemolysed samples. Most insulin assays are calibrated against the standard IRP 66/304 preparation, and the new 83/500 standard is not yet used by all insulin assays. As a consequence of the differences between the standards and the methods employed, the conversion factor from mIU/L to pmol/L varies from 6.0 to 7.5. In the 2009 expert consensus, the threshold of 3 mIU/L is equal to 18 pmol/L.

Insulin concentrations had been measured for long with non-specific assays that yielded cross-reactions with proinsulin. The insulin assays that are now in use have negligible cross-reaction with proinsulin. Though the 3 mIU/L threshold (which replaces a 6 mIU/L threshold previously established with less specific insulin assays) was established for insulin-specific assays, it is known now that the finding of low insulin levels with such assays cannot rule out the diagnosis of insulinoma (Vezzosi et al. 2003). 11-35% patients with insulinoma were found to have insulin levels below the recommended diagnostic threshold (3 mIU/L) at the time of hypoglycemia when insulin was measured with insulin-specific assays, the percentage of values below 3 mIU/L depending on the assay employed (Vezzosi et al. 2007). On the other hand, while the specificity of the 3 mIU/L threshold was found to be 100% with a plasma glucose concentration threshold of 0.45 g/L for the diagnosis of hypoglycaemia related to endogenous hyperinsulinism, it was lowered to 87 % for glucose levels ranging from 0.46 to 0.54 g/L (personal data). The sensitivity and specificity for serum insulin concentrations with a threshold level of at least 3 mIU/L at the time of plasma glucose concentrations below 0.6 g/L were found to be 93% and 95%, respectively (Placzkowski et al. 2009).

C-peptide

C-peptide and proinsulin levels at the time of hypoglycemia have better diagnostic accuracy than insulin levels. C-peptide assays are calibrated against the 1st standard IRP 84/510 (WHO). According to the expert consensus (Cryer et al. 2009), serum C-peptide levels of at least 0.6 ng/mL concomitant with plasma glucose concentrations below 0.55 g/L are one of the criteria that make the diagnosis of hypoglycaemia related to endogenous hyperinsulinism. In 33 patients who reached plasma glucose concentrations below 0.45 g/L during a fast test, all insulinoma patients had C-peptide levels above 0.6 ng/mL, and only one patient who had previously been treated by left-sided pancreatectomy for nesidioblastosis and who had recurrent hypoglycaemia did not reach the 0.6 ng/mL threshold at the time of hypoglycaemia below 0.45 g/L (Vezzosi et al. 2007). The diagnostic accuracy is improved when blood glucose levels drop below 0.45 g/L: for such blood glucose levels, the sensitivity

and specificity of C-peptide (with a threshold of 0.6 ng/mL) are close to 100%, whereas we observed a false positive rate of 9% for C-peptide for concomitant plasma glucose concentrations of 0.46-0.54 g/L (personal data). It had been previously shown that for the 0.50-0.60 g/L (O'Brien et al. 1993) or 0.45-0.60 g/L (Vezzosi et al. 2007) range for plasma glucose concentrations, there was a considerable overlap between patients and controls regarding C-peptide levels. In the study by Placzowski et al. the sensitivity of the 0.6 ng/mL threshold for the diagnosis of insulinoma is 100 % if concomitant plasma glucose is below 0.6 g/L, while its specificity is 60% for concomitant glucose levels below 0.6 g/L and 78% for concomitant glucose levels of 0.5 g/L or less (Placzowski et al. 2009). This argues for prolonging the fast test until a glucose level of 0.45 g/L or less is reached.

Proinsulin

A high proportion of proinsulin is known to be secreted by insulinomas. Intact proinsulin enzymatic processing leads to split 32,33 proinsulin or split 65,66 proinsulin, then to des-31,32-proinsulin (the molecule with the highest serum concentration) and des-64,65-proinsulin and finally to insulin and C-peptide. Proinsulin assays may measure either intact proinsulin (most of them measuring both intact proinsulin and des-64,65-proinsulin) or "total proinsulin" (i.e. intact proinsulin and the other molecules, mostly des-31,32-proinsulin). Therefore the results depend strongly on the method employed. In addition, proinsulin should be measured in serum samples, since results observed in plasma samples may be different (and higher).

According to the 2009 consensus (Cryer et al. 2009), proinsulin levels of at least 5 pmol/L concomitant with plasma glucose concentrations below 0.55 g/L are one of the criteria that make the diagnosis of hypoglycaemia related to endogenous hyperinsulinism. Whether this 5 pmol/L threshold refers to assays measuring "total proinsulin" or "intact proinsulin", or to a specific assay, has not been specified. We used the Human Proinsulin RIA kit (Linco Research), which measures "total proinsulin" (in fact intact proinsulin and des-31,32-proinsulin, the cross-reactions with des-64,65-proinsulin, insulin and C-peptide being < 0.1%), to measure proinsulin in 33 patients with hypoglycaemia related to endogenous hyperinsulinism and 67 controls who underwent a 72-hour fast test. 100% sensitivity and specificity were found using a 5 pmol/L threshold for serum proinsulin and a 0.45 g/L threshold for plasma glucose concentration (Vezzosi et al. 2007). The specificity would have been much lowered if the 5 pmol/L threshold had been applied to the 0.46-0.54 g/L range for plasma glucose concentrations: 9 out of 31 control subjects (29%) who reached this range of plasma glucose concentrations during the prolonged fast were found to have proinsulin levels above 5 pmol/L (personal data). For this threshold of 5 pmol/L, Placzowski et al reported a 100%-sensitivity for the diagnosis with plasma glucose concentrations below 0.6 g/L, whereas the specificity was only 68% and 78% with glucose levels below 0.6 g/L and below 0.5 g/L, respectively (Placzowski et al. 2009). This also argues for prolonging the fast test until a glucose level of 0.45 g/L or less is reached.

In addition, serum proinsulin levels above 22 pmol/L can make the diagnosis of hypoglycaemia related to endogenous hyperinsulinism when concomitant plasma glucose concentration is below 0.6 g/L with 74% sensitivity and 100% specificity. Moreover, in non-obese subjects (body mass index less than 30 kg/m²) the diagnostic specificity of a 22 pmol/L for serum proinsulin levels measured after an overnight fast was found to be 100%, while its sensitivity was 70%, with concomitant low or normal plasma glucose

concentrations (Vezzosi et al. 2007). This 22 pmol/L (0.2 ng/mL) threshold for proinsulin had been previously reported by Hirshberg et al. (Hirshberg et al. 2000). In obese or insulin-resistant subjects, proinsulin levels after an overnight fast exceeding 22 pmol/L do not make the diagnosis of insulinoma: in a group of 110 obese subjects who did not present with glycaemic disorders, 23 (21%) had proinsulin levels above 22 pmol/L after an overnight fast (Vezzosi et al. 2007). In conclusion, serum proinsulin levels after an overnight fast below 22 pmol/L do not rule out the diagnosis of insulinoma, while if they are above 22 pmol/L in a non-obese, non-insulin-resistant subject they should lead to a high suspicion of insulinoma, but to date, this can be used as a diagnostic criterion only if plasma glucose levels do not exceed 0.6 g/L.

There are some limitations regarding the insulin, C-peptide and proinsulin threshold levels for the diagnosis of hypoglycaemia related to endogenous hyperinsulinism.

The recommended diagnostic thresholds for serum insulin, C-peptide and proinsulin levels are known to be valid only in patients with normal liver and renal function, and there is no study regarding their validity in patients who have concurrent endocrine disorders liable to modify insulin resistance or sensitivity and glucose counter-regulation. In addition, there is no specific study regarding their validity for the diagnosis of recurrence of insulinoma after partial pancreatectomy.

In 33 patients with hypoglycaemia related to endogenous hyperinsulinism, the only patient who did not present with a C-peptide level of at least 0.6 ng/mL at the time of hypoglycaemia below 0.45 g/l during a fast test was a patient who had recurrence of nesidioblastosis one year after undergoing left-sided pancreatectomy; we speculated that a lower glucagon production could explain why severe hypoglycaemia was associated with lower insulin and C-peptide levels than in the other patients (Vezzosi et al. 2007). In addition, three of our patients with malignant insulinomas, in whom total remission had been initially achieved by partial pancreatectomy, did not fulfil the criteria for C-peptide levels when they were found to have recurrence of tumour-induced hypoglycaemia (personal data).

Insulin clearance takes place in the liver (50% of portal insulin is cleared by the liver) and in the kidney (50% of peripheral insulin removal) both by diffusion and receptor-mediated transport, the major route of clearance being receptor-mediated degradation by the renal tubular epithelial cells; the kidney also removes 70% of C-peptide by renal filtration. Therefore, measuring insulin and C-peptide levels in patients with severe renal insufficiency is not helpful; in such patients it has been recommended to use beta-hydroxy-butyrate levels and glucose response to glucagon at the end of a fast test to provide evidence for insulin-mediated hypoglycaemia (Basu et al. 2002).

Beta-hydroxy-butyrate

Another valuable tool for the diagnosis of insulinomas is measurement of plasma beta-hydroxy-butyrate level during the fast test. Insulin is known to suppress ketogenesis. According to the 2009 consensus (Cryer et al. 2009), during a fast test, beta-hydroxy-butyrate levels of 2.7 mmol/L or less indicate mediation of hypoglycaemia by insulin.

A progressive rise in beta-hydroxy-butyrate levels during the fast test was found to rule out insulinomas (Service & O'Brien 2005). A plasma level of beta-hydroxy-butyrate exceeding 2.7 mmol/L was found to rule out the diagnosis of insulinoma when blood glucose levels were 0.50-0.60 g/L during a 72-hour fast test with both sensitivity and specificity close to

100% (O'Brien et al. 1993). There is no study specifying the validity of this criterion for another range of plasma glucose concentrations. Placzowski et al. reported 100% sensitivity and specificity for the diagnosis of insulinoma with beta-hydroxy-butyrate levels of 2.7 mmol/L or less during a fast test with concomitant plasma glucose concentrations below 0.6 g/L or below 0.5 g/L (Placzowski et al. 2009), but the results are not detailed. There are two case reports of insulinoma patients with false negative results of beta-hydroxy-butyrate levels: an 80-year-old female patient with plasma glucose concentrations of 0.48 g/L (2.7 mmol/L), serum C-peptide of 0.93 ng/mL (0.31 nmol/L) and beta-hydroxy-butyrate levels of 3.0 mmol/L after 72 hours of fast (Wiesli et al. 2004b) and a 49-year-old man with plasma glucose concentrations of 0.32 g/L, serum C-peptide levels of 1.2 ng/mL, and beta-hydroxy-butyrate levels of 3.2 mmol/L (Soh & Kek 2010). Among our patients (Vezzosi et al. 2007), one patient with a malignant insulinoma was found to have, during a fast test, plasma glucose concentrations of 0.36 g/L, serum C-peptide levels of 1.7 ng/mL, plasma proinsulin levels of 37 pmol/L (which led to the unequivocal diagnosis of inappropriate insulin secretion) and plasma beta-hydroxy-butyrate levels of 3.8 mmol/L. We hypothesized that severe hypoglycaemia below 0.45 g/L could result in a greater secretion of counter-regulatory hormones thereby leading to an increase in beta-hydroxy-butyrate levels; lipolysis may escape the inhibitory effect of insulin during hyperinsulinic hypoglycaemia (Lucidi et al. 2010). However we observed a patient with a malignant insulinoma whose lowest plasma glucose concentration during a 72 hour-fast test was 0.53 g/L after 58 hours of fast, with concomitant serum levels of insulin, C-peptide and proinsulin of 13 mIU/L, 2.4 ng/mL, and 36 pmol/L (which gave diagnostic evidence), respectively, and plasma beta-hydroxy-butyrate levels above 2.7 mmol/L. At the end of the 72 hour-fast test, beta-hydroxy-butyrate levels reached the value of 7.0 mmol/L in this patient, with concomitant concentrations of 0.68 g/L for plasma glucose, 4.0 mIU/L for serum insulin, 1.2 ng/mL for serum C-peptide and 25 pmol/L for serum proinsulin (personal data).

In conclusion, though being very valuable, the threshold of 2.7 mmol/L or less for beta-hydroxy-butyrate levels does not yield 100% sensitivity and specificity. Based on the observed results there are several caveats: 1) beta-hydroxy-butyrate levels may lose part of their diagnostic accuracy when plasma glucose concentrations are below 0.45 g/L and are of minor interest for this range of glucose levels; 2) proinsulin levels must be taken into account before ruling out the diagnosis of insulinoma in patients whose plasma glucose concentrations are within the 0.45-0.60 g/L range even when plasma beta-hydroxy-butyrate levels reach values above 2.7 mmol/L; 3) patients with recurrent insulinoma or nesidioblastosis after partial pancreatectomy may not fulfil the usual diagnostic criteria for insulin-mediated hypoglycaemia during the fast test. Whether a disruption in the progressive elevation of beta-hydroxy-butyrate levels concomitant with lower glucose levels during the fast test (with an insulin secretory burst) should lead to suspicion of insulinoma remains to be determined.

Glucagon test

According to the 2009 expert consensus (Cryer et al. 2009) an increase in plasma glucose of at least 25 mg/dL (0.25 g/L, 1.4 mmol/L) after intravenous glucagon indicate mediation of hypoglycaemia by insulin. This refers to the evaluation protocol established by the Mayo Clinic group (O'Brien et al. 1993) : the glucagon test is performed at the end of a prolonged fast test, i.e. either at the time of occurrence of symptomatic hypoglycaemia with concomitant

plasma glucose concentrations of 0.45 g/L (2.5 mmol/L) or less, or after 72 hours of fast: plasma glucose responses to the intravenous injection of 1 mg glucagon are measured at 10 min-intervals for 30 min. Under these conditions, plasma glucose response to glucagon was found to be higher in insulinoma patients than in controls with a range of maximal increase in plasma glucose concentrations of 1.4-5.4 mmol/L in insulinoma patients and of 0.1-1.3 mmol/L in controls, as a consequence of a lesser depletion of hepatic glycogen in insulinoma patients during the fast, which is related to the higher insulin secretion in the patients. This allowed a clear distinction between patients and controls who has reached plasma glucose concentrations below 3.3 mmol/L (0.6 g/L) during the fast test (O'Brien et al. 1993).

On the other hand, the glucagon test has long been known to be a provocative test in insulinoma patients: glucagon may trigger severe hypoglycaemia related to insulin secretion in insulinoma patients. This provocative test was found to be helpful for the diagnosis of insulinoma in patients with a negative fast test (Wiesli et al. 2004b; Soh & Kek 2010).

Other diagnostic criteria for hypoglycaemia related to endogenous hyperinsulinism

* Regarding the various tests employed in the evaluation of a patient with suspected hypoglycaemic disorder, only the fast test, with a glucagon test at its termination, in patients with symptoms of fasting hypoglycaemia, and the mixed meal test in patients with postprandial hypoglycaemia are recommended by the 2009 expert consensus (Cryer et al. 2009).

Physical exercise is known to result in hypoglycaemia in many insulinoma patients. A physical exercise was found to be necessary in some insulinoma patients to make the correct diagnosis (Jarhult et al. 1981). The percentage of patients with negative fast test and meal test who could be diagnosed to have insulinoma by a physical exercise test remains to be established. In selected patients a "physical exercise test" under medical supervision, with at least serial measurements of plasma glucose and serum insulin, C-peptide and proinsulin could be considered.

Cohn's diet (1200 kcal with 50 g of carbohydrates followed by a 36 hour-fast) is no more in use and has been replaced by the 72 hour-fast test.

The oral glucose tolerance test was found to be of interest in patients with a negative fast test (Wiesli et al. 2004b) (Kar et al. 2006), but it was shown to be less accurate than the mixed meal test (Hogan et al. 1983) and is not recommended by the 2009 expert consensus (Cryer et al. 2009). 10% of healthy persons were reported to have a plasma glucose nadir less than 0.5 g/L during this test while being asymptomatic and without presenting with Whipple's triad (Lev-Ran & Anderson 1981). Whether such subjects may have some subtle abnormality regarding glucose regulation may still be debated, but this test was not considered as a tool to provide diagnostic evidence for a hypoglycaemic disorder.

The C-peptide suppression test by insulin-induced hypoglycaemia may give results that do not clearly distinguish all patients from controls, and its interpretation may be difficult, since the results depend on several parameters including gender and body mass index (Service et al. 1992). A more sophisticated C-peptide suppression test, combined with the euglycaemic clamp, was successfully employed for the diagnosis of insulinoma, but it cannot be recommended for clinical practice (Gin et al. 1987).

* Regarding the diagnostic criteria for inappropriate insulin secretion, previously employed ratios (insulin/glucose ratio, Turner's index) are no more in use and do not bring greater diagnostic accuracy than the presently-used criteria (Vezzosi et al. 2007) (Service 1995). Though insulinoma secrete a high proportion of proinsulin, the proinsulin/insulin ratio

does not bring more valuable information than proinsulin levels for the diagnosis of insulinoma (Vezzosi et al. 2007).

2.2 Differential diagnosis

2.2.1 Evaluation of the patient

In an adult patient clinically otherwise healthy who presents with severe hypoglycemia, the diagnosis of insulinoma must be considered as very likely, provided that the patient does not use insulin or other hypoglycaemic agents.

Apart from “reactive functional hypoglycaemia”(see below), which is a controversial and heterogeneous medical entity without actual hypoglycaemia below 0.55 g/L, other actual causes of hypoglycaemia are often observed in patients presenting with other clinical symptoms related to their disease: alcohol ingestion, critically ill patients or septicemia, severe prolonged undernutrition, liver or renal deficiency, adrenal insufficiency, hypopituitarism, IGF-II or pro-IGF-II secreting tumours, or very rare patients with other tumour secretion (IGF-I, GLP1 and somatostatin).

Thus the first step is to record carefully the history of the patient including exposure to any medication, and the possible access to hypoglycaemic agents, and to perform a clinical physical examination.

Then the causes of hypoglycaemia are identified mainly on the basis of insulin, C-peptide and proinsulin levels at the time of hypoglycaemia. Additional biological evaluation comprises measurement of oral hypoglycaemic agents (at the time of hypoglycaemia) and anti-insulin antibodies (at any time) in plasma samples in patients who are found to have insulin-mediated hypoglycaemia. Other plasma measurements will be made if there is clinical presumption of a specific disease, for instance diseases known to lead to hypoglycaemia mediated by IGF-II or incompletely processed IGF-II (“big IGF-II”), exceptionally IGF-I. Finally, according to the 2009 expert consensus (Cryer et al. 2009), “a test of adrenocortical function is reasonable”.

2.2.2 Reactive “functional hypoglycaemia”

Reactive “functional hypoglycaemia” is a controversial entity, and its existence is still debated. The first definition of “reactive functional hypoglycaemia” had been based on the belief that hypoglycaemic disorders could be divided into disorders responsible for fasting hypoglycaemia (mainly insulinoma) and disorders responsible for reactive hypoglycaemia (mainly “functional hypoglycaemia”). It is now known that many organic disorders may result both in fasting and/or reactive hypoglycaemia. However, many patients present with dizziness or minor autonomic symptoms within the hours following a meal, and most of them do not meet the criteria for actual hypoglycaemia, i.e. they do not have actually low plasma glucose levels below 0.55 g/L, and do not necessarily fulfil Whipple’s triad. The so-called “reactive functional hypoglycaemia” may be the only likely diagnosis for some of these patients, but glucose levels do not drop below 0.55 g/L, and it cannot be responsible for symptoms of neuroglycopenia. It could reflect various mechanisms: 1) rapid changes in plasma glucose concentrations after ingestion of nutrients with a high glycaemic index; 2) a plasma glucose threshold for autonomic symptoms higher than that of other subjects 3) various reactions after ingestion of nutrients, including mechanisms differing from changes in plasma glucose levels. The patients are asked to reduce their intake of simple carbohydrates while increasing that of complex carbohydrates, and to divide their daily

nutrient intake into three meals and two or three snacks. Repeated symptoms suggesting hypoglycaemia despite correct nutrition warrant further investigation.

Actual reactive insulin-mediated hypoglycaemia is observed in patients with dumping syndrome (see below, causes of hypoglycaemia differing from insulinomas), and this must be distinguished from “reactive functional hypoglycaemia”.

2.2.3 Causes of hypoglycaemia differing from insulinomas

Medications known to be used by the patient

The first step of any evaluation is to check whether some of the medications ordered to the patient can cause hypoglycaemia. Insulin, insulin analogues or insulin secretagogues (sulfonylureas, glinides) are the most common causes of hypoglycaemia. Some patients may be mistaken and accidentally take inappropriate doses of medications, or undergo concurrent disorders that increase the bioavailability of the drug. Though metformin cannot induce hypoglycaemia, as confirmed by the expert consensus (Cryer et al. 2009), it has been reported to cause severe hypoglycaemia in the 1995 UK prospective diabetes study (Cryer et al. 2009) and in an elderly patient (Zitzmann et al. 2002). Thiazolidine-diones, alpha-glucosidase inhibitors, GLP1-receptor agonists and dipeptidyl peptidase IV inhibitors do not induce hypoglycaemia themselves but increase the risk of hypoglycaemia when combined with an insulin secretagogue or insulin. Other medications are known to be liable to induce hypoglycaemia, mostly in aged patients and patients with associated diseases, or combination of treatments, or renal failure. Miscellaneous mechanisms may be involved: increased insulin release, reduced insulin clearance, interference with glucose metabolism, liver or renal toxicity (Ben Salem et al. 2011).

A list of the most commonly employed medications liable to induce hypoglycaemia has been given in the 2009 consensus (Cryer et al. 2009): some of them are associated with a risk of hypoglycaemia with moderate quality of evidence: cibenzoline, gatifloxacin, pentamidine, quinine, indomethacin. Other medications are involved with a lesser quality of evidence. The most commonly reported offending drugs appeared to be quinolones, pentamidine, quinine, beta blockers, angiotensin-converting enzyme agents, and IGF (Murad et al. 2009). Salicylates in large doses (4-6 g/day) may produce rarely hypoglycaemia in adults, and more often in children, by reducing basal glucose production and possibly increasing sensitivity to insulin (Cryer 2008). Disopyramide (Marks & Teale 1999), non-steroid anti-inflammatory drugs, analgesics, antidepressants (Ben Salem et al. 2011) and antifungal agents (Lionakis et al. 2008) have been reported to induce hypoglycaemia. However hypoglycaemia appears to be rare with such medications, unless employed in combination with other medications or in patients with underlying diseases. Recently tyrosine kinase inhibitors were found to decrease plasma glucose concentrations (Agostino et al. 2010). Patients with huge non functional endocrine tumours and multiple liver metastases may be at risk of developing hypoglycaemia when treated by long-acting somatostatin analogues, as a result of reduced glucagon and GH secretion, impairment of hepatic glucose output and delay in intestinal absorption of carbohydrates (Unek et al. 2009).

Patient with known or obvious acute or chronic disorder

In such patients the diagnosis is often clinically obvious. Concurrent intake of hypoglycaemic agents must always be screened for, and in patients without any treatment

with insulin secretagogues, measurement of insulin, C-peptide, proinsulin and (whenever possible) beta-hydroxy-butyrate levels at the time of hypoglycaemia below 0.55 g/L will generally rule out insulin-mediated hypoglycaemia, unless the underlying disorder (especially in renal failure and acute liver failure) is liable to alter insulin, C-peptide and proinsulin metabolic processing and clearance.

Alcohol

Alcohol ingestion is known to cause hypoglycaemia. Serum insulin and C-peptide are appropriately low during episodes of alcohol-induced hypoglycaemia (Marks & Teale 1999). Ethanol inhibits gluconeogenesis (Cryer 2008) and hormonal counterregulation to hypoglycaemia (Marks & Teale 1999; Cryer 2008), and can exert influences on pancreatic microcirculation, resulting in a massive redistribution of blood flow from the exocrine into the endocrine part of the pancreas, augmenting late-phase insulin secretion (Huang & Sjöholm 2008). In patients presenting in coma from alcohol-induced hypoglycaemia, recovery after glucose injection is immediate, with no relapse if there is no concurrent cause of hypoglycaemia; recovery is delayed when brain swelling has occurred, which requires specific treatment. Glucagon is not recommended (Marks & Teale 1999). Alcohol-induced hypoglycaemia typically occurs after a binge of alcohol consumption within 6 to 36 hours generally in a patient who presents glycogen depletion, and ethanol is measurable in blood but poorly correlates with glucose levels; it may also be a late feature of alcoholic keto-acidosis and ethanol may be undetectable in blood samples (Marks & Teale 1999).

Acute hepatic failure

Acute hepatic failure, with massive and rapid liver destruction, rather than common forms of cirrhosis and hepatitis, can lead to severe hypoglycaemia. Massive destruction of the liver tissue and defective glucose storage in extrahepatic organs are thought to be the main mechanisms, but non-insulin hypoglycaemic factors secreted by the damaged liver might be involved, since reversal of fulminant hepatitis-associated hypoglycaemia was observed at the anhepatic stage of liver transplantation (Ilan et al. 1996).

Renal failure

Hypoglycaemia is not rare in renal failure and its pathogenesis involves generally several mechanisms (Arem 1989; Basu et al. 2002). Mechanisms directly related to renal failure are involved: reduced renal gluconeogenesis, impaired renal insulin degradation and clearance. Additional mechanisms may be involved, such as medications, sepsis, poor nutrition with deficiency of precursors of gluconeogenesis, impaired glycogenolysis, defective counterregulation with frequent autonomic dysfunction, concurrent disorders such as concomitant liver disease, congestive heart failure, or an associated endocrine deficiency. In patients undergoing haemodialysis a particular mechanism is postdialysis glucose-induced hyperinsulinemia, caused by a high glucose content in the dialysate (Arem 1989; Basu et al. 2002). On the other hand dialysis with glucose-free solution results in frequent hypoglycaemia, whereas using glucose-added dialysis solution at 90 mg/dL was found to reduce the number and severity of hypoglycaemic episodes (Burmeister et al. 2007). Since clearance of insulin, C-peptide and proinsulin is impaired in renal failure, beta-hydroxy-butyrate during a fast test and glucose response to glucagon were reported to be the best biological parameters for the differential diagnosis of insulinoma in patients with renal failure (Basu et al. 2002).

Heart failure

Hypoglycaemia has been occasionally reported in patients with congestive heart failure. Its pathogenesis is unknown, probably multifactorial, and may involve inhibited gluconeogenesis (Cryer 2008).

Inanition

Inanition related hypoglycaemia, with low insulin, C-peptide and proinsulin levels has been found in some patients with very severe malnutrition, such as patients with very severe chronic anorexia nervosa (Rich et al. 1990; Yanai et al. 2008). The occurrence of inanition-related severe hypoglycaemia in a patient with anorexia nervosa is thought to imply a grave prognosis (Rich et al. 1990).

Adrenal or pituitary failure

Adrenal and/or pituitary failure does not result in plasma glucose concentrations below 0.55 g/L unless associated with other disorders or hypoglycaemic medications. Plasma glucose concentrations of 0.6 g/L may be found in such patients, and are often associated with hyponatremia and/or typical clinical symptoms of the disease. As stated in the 2009 expert consensus (Cryer et al. 2009), adrenocortical failure without associated conditions is unlikely to induce hypoglycaemia below 0.55 g/L, and a low cortisol level at the time of hypoglycaemia may be the consequence of a lower glycaemic threshold to stimulate cortisol in patients with recurrent hypoglycaemia without adrenal failure.

Other causes**Low insulin, C-peptide and proinsulin levels**

* Hypoglycaemia related to non-insulin secreting tumours : IGF-II and precursors ("big IGF-IIs")

If insulin, C-peptide and proinsulin levels are low at the time of hypoglycemia, the diagnosis of non pancreatic IGF-II (or pro-IGF-II) -secreting tumour must be considered. However, one must bear in mind that rare insulin-specific assays may not be able to identify insulin analogues (see below, "factitious hypoglycaemia"). Patients with IGF-II secreting tumours have low IGF-I levels and increased IGF-II/IGF-I ratios, which are pathognomonic of the diagnosis. IGF-II precursors ("big IGF-IIs") do not complex normally with IGFBPs, thus can reach more readily target tissues, which is thought to be the mechanism of hypoglycaemia in most patients. Enhanced mRNA expression of IGF-II and defective expression of prohormone convertase 4, a potential protease responsible for IGF-II precursor processing, were found in a patient with pleural solitary fibrous tumour (Tani et al. 2008). Glucose consumption is also thought to be a mechanism of hypoglycaemia in such tumours, and could be the major mechanism in some patients without evidence for IGF-II secretion, in whom PET-scan with 18-Fluoro-deoxy-glucose showed preferential tumour glucose uptake (Habra et al. 2010). Most IGF-II secreting tumours are large tumours that can be found on clinical examination or chest X-ray. IGF-II related hypoglycaemia is well known in patients with pleural solitary fibrous tumour (Doege-Potter syndrome). Solitary fibrous tumour is a rare mesenchymal neoplasm composed of CD34-positive fibroblastic cells; it can be either pleural or extrapleural, with abdominal locations, of whom one was found to grow in the bladder (Bruzzone et al. 2010). IGF-II secreting mesenchymal neoplasms are numerous, and also comprise synovial sarcomas, myxoid liposarcomas, GISTs, malignant peripheral nerve sheath tumours, chondrosarcomas, undifferentiated pleomorphic sarcomas, Ewing's

sarcomas and tenosynovial giant cell tumours (Steigen et al. 2009) . We observed hypoglycaemia with suppressed insulin, C-peptide and proinsulin levels and high pro-IGF-II levels in a patient with a malignant meningioma and lung and pleural metastases (unpublished observation). Rare cases of adrenocortical carcinomas have also been reported to be responsible for hypoglycaemia (Cryer 2008). One exceptional patient with an islet-cell tumour of the pancreas was reported to have IGF-II-related hypoglycaemia (Chung et al. 2008).

*** Other tumours (non-insulin, non-IGF-II secreting tumours)**

Exceptionally, tumour-induced hypoglycaemia was found to be related to hormone secretions that differed from insulin or IGF-II: IGF-I, in a metastasizing undifferentiated large-cell carcinoma of the lung (Nauck et al. 2007), somatostatin in an ovarian teratoma (Gregersen et al. 2002). The latter patient had alternate episodes of hyper- and hypoglycaemia, with only reactive post-prandial hypoglycaemia and a negative fast test; insulin levels were low at the time of hyperglycaemia, and were not reported at the time of hypoglycaemia. It was hypothesized that somatostatin led to suppression of glucagon secretion to a greater extent than that of insulin secretion in the post-prandial period, thereby leading to reactive hypoglycaemia. Another ovarian tumour was reported to induce hypoglycaemia by secreting GLP-1 and somatostatin (see below).

High insulin levels with low C-peptide and proinsulin levels

*** Factitious hypoglycaemia related to insulin and insulin analogues**

In clinical practice, the finding of high insulin levels with concomitant low C-peptide and proinsulin levels is almost specific of the diagnosis of surreptitious insulin injections (Grunberger et al. 1988). It must be known that some insulin-specific assays may not be able to identify insulin analogues (Sapin 2003; Neal & Han 2008); insulin assays that can identify the presence of insulin analogues are to be preferred.

*** Anti-insulin receptor antibodies**

Such antibodies were found mostly in patients with immunity disorders, either before or after the use of medications like methimazole (Redmon & Nuttall 1999). Many of these patients have type B insulin resistance and diabetes mellitus, but some of them develop hypoglycaemia. Anti-insulin receptor antibodies bind to the insulin receptor, may mimic insulin action and cause fasting hypoglycaemia; also, they may inhibit insulin binding thereby inhibiting insulin clearance and increasing insulin levels, while the resulting hypoglycaemia suppresses beta-cell secretion and C-peptide levels (Taylor et al. 1989). Spontaneous remissions and improvement after glucocorticoid treatment have been reported (Taylor et al. 1989).

*** Insulin receptor mutation**

Exceptionally patients may present an insulin receptor mutation, which is transmitted as an autosomal dominant trait, and delays insulin clearance, resulting in hypoglycaemia with inappropriate insulin levels after an overnight fast, and low C-peptide levels, with increased insulin/C-peptide ratio (Hojlund et al. 2004), or reactive insulin-mediated hypoglycaemia; in such patients the fast test is positive for hypoglycaemia (< 0.4 g/L), but insulin, C-peptide and proinsulin are suppressed during a prolonged fast. This disease can be considered to be one of the established genetic causes of nesidioblastosis (see below).

High insulin, C-peptide and proinsulin levels

If insulin, C-peptide and proinsulin levels are elevated at the time of hypoglycemia, insulinoma is the most likely diagnosis. One must remind that some insulinoma patients do not have elevated insulin levels when insulin is measured with insulin-specific assays (Vezzosi et al. 2003). When an insulinoma is not found by imaging techniques, two very different diagnoses must be suspected: factitious hypoglycemia related to sulfonylurea or glinide, or nesidioblastosis, which is rare in adult patients. Exceptionally, anti-insulin antibodies and extra-pancreatic non-islet cell insulin-secreting tumours may also be found; sometimes a genetic metabolic disorder which has been overlooked at a younger age may be diagnosed in an adult patient. Finally, a particular condition is reactive insulin-mediated hypoglycaemia in patients with dumping syndrome; some of these patients were reported to have post-gastric bypass nesidioblastosis.

*** Factitious hypoglycaemia related to sulfonylureas or glinides**

A plasma sample must be collected to measure oral hypoglycaemic agents (ideally all available sulfonylureas and glinides) with specific methods at the time of symptomatic hypoglycaemia. This is the only way to distinguish factitious (or accidental) hypoglycaemia related to insulin secretagogues from the endogenous abnormal insulin secretion observed in patients with insulinomas and nesidioblastosis. The diagnosis is generally suspected in patients whose relatives are diabetic or health professionals, but it may be very difficult (Hirshberg et al. 2001).

*** Anti-insulin antibodies**

Anti-insulin antibodies responsible for hyperinsulinaemic hypoglycaemia have been rarely found (Taylor et al. 1989; Redmon & Nuttall 1999) generally in patients with autoimmune disorders who developed such antibodies spontaneously or a few weeks after specific treatments for autoimmune diseases, especially medications with a sulphydryl group, or in very rare cases of myeloma (Halsall et al. 2007). Anti-insulin antibodies must be measured in patients with hypoglycaemia related to endogenous hyperinsulinism, not necessarily during hypoglycaemia (Cryer et al. 2009). Insulin levels are often very high, partly as a consequence of an interference in the insulin assay by the anti-insulin antibody. Most patients have reactive hypoglycaemia, which could be a consequence of meal-induced exaggerated insulin secretion, overcoming the buffering effect of the antibody (Taylor et al. 1989); however some patients also have fasting hypoglycaemia (Basu et al. 2005). The natural course is not predictable, some patients may be controlled by frequent meals and many experienced remission some months after the withdrawal of the drug responsible for the onset of the disorder, but others required glucocorticoids or even plasmapheresis.

*** Non islet cell insulin -secreting tumours and GLP-1 secreting tumour**

Non islet cell insulin-secreting tumours are quite exceptional. They must be distinguished from “ectopic insulinomas” which are extrapancreatic islet-cell tumours located in the proximity of the pancreas. Insulin-mediated hypoglycaemia has been reported in the following tumours : a small cell carcinoma of the cervix (Seckl et al. 1999), a neuroectodermal brain tumour (Nakamura et al. 2001), and a neuroendocrine carcinoma of the gallbladder (Ahn et al. 2007).

Todd et al reported a GLP-1 and somatostatin-secreting ovarian tumour (Todd et al. 2003). The patient had alternate episodes of hyper- and hypoglycaemia, with a negative fast test.

Insulin-mediated hypoglycaemia was thought to be a consequence of GLP-1 and somatostatin secretion; since the effects of GLP-1 on insulin secretion are dependent on glucose levels, the inhibitory effects of somatostatin on glucagon secretion may have played a role in inducing reactive hypoglycaemia.

*** Genetic metabolic disorders**

Some patients with hypoglycaemia related to metabolic genetic disorders may occasionally be diagnosed to have such disorders when they are adults. Some of these disorders can be considered as possible causes of nesidioblastosis (Christesen et al. 2008; Palladino & Stanley 2011) (Flanagan et al. 2011b) (Flanagan et al. 2011a) (see last section of this chapter): 1) physical exercise-induced hypoglycaemia caused by failed silencing of monocarboxylate transporter 1 in pancreatic beta cells; 2) patients with mostly post-prandial (but also fasting) symptoms of hypoglycaemia in mutations of insulin receptor (see above), activating mutation of glucokinase with some patients diagnosed only as adults (Christesen et al. 2008), and hyperinsulinism-hyperammonemia syndrome due to activating mutations of glutamate dehydrogenase; 3) patients with mostly fasting (and also post-prandial) hypoglycaemia due to mutations in the genes of the subunits of K-ATP channel (ABCC8, KCNJ11) and mutations of 3-hydroxy-acyl-CoA dehydrogenase (HADH) gene. Among 79 patients admitted in our department between 1990 and 2010 for organic causes of hypoglycaemia (69 of them with insulinomas) only one had hyperinsulinism-hyperammonemia syndrome (diagnosed at the age of 30), with an activating mutation of glutamate dehydrogenase, and another one had two heterozygous mutations of the ABCC8 gene (diagnosed at the age of 47). Both patients had been treated since early childhood for epilepsy.

Other patients may present with other metabolic disorders such as disorders of the glycogen metabolic pathway. Some patients with almost asymptomatic forms of glycogen storage disease type Ia may develop hepatocellular adenomas and carcinomas as adults (Cassiman et al. 2010).

A detailed review of these genetic disorders in childhood has been made by Palladino (Palladino et al. 2008).

*** Reactive hypoglycaemia in patients with dumping syndrome**

Postprandial hypoglycaemia caused by rapid emptying of the gastric remnant has long been known to be a possible complication of gastric resection; it is associated with various symptoms, including symptoms unrelated to hypoglycaemia, which are termed dumping syndrome. Many, but not all patients with post-gastric bypass were found to have reactive severe insulin-mediated hypoglycaemia a few months or years after bypass surgery. Continuous glucose monitoring can be a useful tool to identify hypoglycaemia in patients after bariatric surgery (Hanaire et al. 2010). The abnormal insulin responses to intraarterial calcium injection and the histopathological findings in 6 patients, compared to pancreata from patients with pancreatic cancer, led to the conclusion that such patients might have gastric bypass-induced nesidioblastosis (Service & O'Brien 2005) (see below). This conclusion was challenged, since Meier JJ et al. did not confirm the histopathological diagnosis of nesidioblastosis in the 6 patients, when compared to pancreata collected at autopsy; they only observed a greater beta-cell nuclear diameter than in controls, and this nuclear diameter was positively correlated with BMI, if the BMI used for the patients in the correlation was the BMI observed prior to bypass surgery (Meier et al. 2006). Goldfine AB et al reported increased GLP-1 levels after a liquid mixed-meal in patients who had post-gastric bypass surgery hypoglycaemia, in comparison with those who did not have

hypoglycaemia (Goldfine et al. 2007). GLP-1 is thought to be unable to induce hypoglycaemia in patients with normal beta cells, but high GLP-1 levels might override glucose-dependency and cause hypoglycaemia (Toft-Nielsen et al. 1998). The degree of post-prandial GLP-1-induced glucagon suppression (which is also dependent on glucose, GLP-2 and GIP levels) might play a role in the resulting post-prandial glucose levels. Insulin-mediated hypoglycaemia after gastric bypass surgery is not associated with overexpression of GLP-1 receptor in islets (Reubi et al. 2010). McLaughlin et al reported immediate reversal of reactive hypoglycaemia by feeding a patient with Roux-en-Y gastric bypass through a gastrostomy tube, which argued against a structural pancreatic abnormality in this patient and provided major evidence for a functional dysregulation of post-prandial insulin secretion in patients with gastric bypass-induced hypoglycaemia (McLaughlin et al. 2010). Nevertheless such patients often require insulin-suppressing treatments (diazoxide, calcium channel blockers, somatostatin agonists) (Tack et al. 2009) (Vella & Service 2007). Acarbose, which delays absorption of simple carbohydrates and may reduce GLP-1 secretion, was successfully employed (in combination with dietary advices) (Tack et al. 2009; Hanaire et al. 2010) but it was found relatively ineffective by others (Vella & Service 2007). A patient who had dumping syndrome after partial gastric resection was finally admitted in our department, 20 years after gastric surgery, for severe reactive insulin-mediated hypoglycaemia, with a negative fast test, and normal pancreas on CT-scan; hypoglycaemia was controlled by diazoxide, not by octreotide. Partial (distal) pancreatectomy has been performed to control hypoglycaemia in some of these patients, as in patients with nesidioblastosis. Since insulinomas may present with GIP and/or GLP-1 receptors, occurrence of insulin-mediated hypoglycaemia after bypass surgery or gastrectomy can be caused by an insulinoma. Radiological evaluation is of course mandatory in such patients.

2.3 Topographic assessment

The topographic assessment of an insulinoma must be performed only after the biological diagnosis of hypoglycemia related to inappropriate insulin secretion has been confirmed. Insulinomas are generally thought to be difficult to localize due to their small size. Intra-operative palpation and ultrasound examination of the pancreas had been thought to be the best methods to detect insulinomas. Using such methods intra-operatively remains mandatory, but to date careful radiological examination must be performed to localize insulinomas before surgery in order to avoid failure of surgery to cure the disease and re-operations. The imaging techniques now in use have greatly improved, so that most insulinomas are detected preoperatively.

High definition multidetector helical CT-scans have become widely available since the early 2000s, so that CT-scan is now again the first examination that must be performed to localize insulinomas. Multidetector CT-scan allows optimization of the scan protocols (with very rapid scan times reducing movement artefacts), and arterial and portal venous phase images on thin-sections. A meticulous technique is mandatory and detailed recommendations have been made regarding the examination procedure (Rockall & Reznick 2007) (Sundin et al. 2009). Most insulinomas are small, isodense with the pancreas on pre-contrast images, then hypervascular on arterial phase images, but sometimes are more easily detected on portal venous phase images. More rarely, the tumours are hyperdense to the pancreas, or have nodular calcification, or appear hypovascular, cystic or hypodense after injection of contrast medium. Exceptionally, ectopic insulinomas are located in the proximity of the pancreas or

of the liver. While the sensitivity of non helical CT had been 29%, with multidetector helical CT-scan a meticulous technique can result in 94 % sensitivity (Rockall & Reznick 2007). CT-scan can show metastases (see below, malignant insulinomas)

MRI is often complementary to CT, in order to confirm a suspected lesion on CT, or to search for a tumour that CT-scan has not been able to localize; combining both methods (CT and MRI) improves the accuracy for detection of insulinomas. Detailed technical information has been provided (Rockall & Reznick 2007). Temporal resolution and spatial resolution are greater with CT than with MRI, but MRI allows high resolution contrast-enhanced imaging. Pancreatic endocrine tumours generally appear hypo-intense on T1-weighted sequences and hyperintense on T2-weighted sequences. On pre-contrast imaging, fat suppressed T1 and fat saturation T2 may improve visualization of the tumours, which appear of low intensity on T1 and have a bright T2 signal. There is a marked homogeneous enhancement after injection of gadolinium, which may in some cases render the low-intensity tumour isointense and less detectable (Rockall & Reznick 2007). The sensitivity of MRI for detection of pancreatic endocrine tumours was first reported to be less than that of CT, but is now similar to that of CT: a sensitivity of up to 94% has now been reported (Thoeni et al. 2000). MRI has also proven very helpful in the diagnosis of hepatic metastases of malignant insulinomas (see below, malignant insulinomas).

Trans-abdominal ultrasound examination is traditionally thought to be of low sensitivity to detect pancreatic endocrine tumours like insulinomas: the sensitivity was as low as 20 % in the series reported in the 1990s, with a maximum of 66-80% (Grant 1999). Insulinomas generally appear as small hypoechoic solid masses. The limitations of ultrasound examination are related to body habitus and tumour size; also, the presence of bowel obscures the left upper quadrant, and insulinomas located in the body and the tail of the pancreas may be difficult to visualize. Water intake by the patient allows to use the stomach as an acoustic window and may improve the detection. A sensitivity of up to 79.3% has been reported with recent material for transabdominal ultrasound (Oshikawa et al. 2002) (Rockall & Reznick 2007).

More recently, contrast-enhanced ultrasonography has been reported to detect insulinomas in a high number of patients. Very promising results were found by An L et al (An et al. 2010), who reported the results obtained with a second-generation sonographic contrast agent (SonoVue) in 31 patients with hypoglycaemia related to endogenous hyperinsulinism, among whom 27 had a solitary insulinoma, 3 had multiple insulinomas, and 1 had no definite tumour during laparoscopic evaluation. The results of contrast-enhanced ultrasonography were in agreement with surgical findings except in three patients: one solitary tumour had been localized in the head of the pancreas and was found in the duodenum ligament; one tumour had been visualized whereas no tumour was found during surgery; in the patient with 6 insulinomas, only 2 tumours had been visualized. Thus the diagnostic sensitivity and localization specificity were 33 (89.2%) and 32 (86.5%) of 37 surgically verified insulinomas, respectively. The enhancement pattern of insulinoma was fast wash-in and slow wash-out. The insulinomas displayed homogeneous hypervascularity in the earlier arterial phase and had still a hyperenhancing pattern in the late phase. This ultrasound non invasive examination could probably be developed in the next years.

Endoscopic ultrasound has been reported to be the reference method to localize insulinomas in the 1990s: it allows to use a high frequency US probe in close proximity to the pancreas, and in expert hands its sensitivity has been shown to be 79-100% (Rosch et al. 1992) (McLean & Fairclough 2005). It may show very small tumours (about 3 mm in size) in the head of the

pancreas, such tumours being impalpable at surgery. A lower sensitivity for pancreatic tail lesions (37-50%) has been reported (Ardengh et al. 2000). Pancreatic nodularities may be mistaken for insulinomas (Kann et al. 2003). Endoscopic ultrasound is an invasive method, which requires sedation, and its results are operator-dependent. Therefore it is now a second-line examination after conventional imaging. Even if recent CT-scan techniques lead to localization of most insulinomas, endoscopic ultrasound still brings the advantage of making a better evaluation of the lesions (especially if they are multiple, as often in MEN-1) and of their proximity with pancreatic ducts and vessels, and it also enables the operator to make biopsies.

Intra-operative ultrasound is mandatory during surgery of insulinomas in order to localize impalpable tumours. High-frequency intra-operative ultrasound has been shown in expert hands to improve detection of small tumours in the pancreatic head and multiple pancreatic lesions to up to 97% (Grant 1988) (Grant 1999). Intra-operative ultrasound examination of the pancreas is also mandatory (using a specific material) during laparoscopic surgery of insulinomas. Despite the high sensitivity of intra-operative ultrasound, a thorough pre-operative examination is necessary to localize insulinomas, in order to maximize the chance for a successful initial resection, minimize the risk of re-operation with its possible morbidity, help in the choice of the surgical technique and make laparoscopic surgery easier when it appears to be the possible choice to remove the insulinoma.

Nuclear imaging of insulinomas is also possible. One of the first functional imaging method was based on the fact that most endocrine tumours display somatostatin receptors, which led to the use of Octreoscan* scintigraphy (111In-DTPA-octreotide). On the other hand, sst2A receptors were found in only about 66% of insulinomas (Reubi & Waser 2003). Recommendations have been made regarding the protocol (Balon et al. 2001; Bombardieri et al. 2003). Because of competition of the somatostatin analogues at the receptor site, somatostatin analogue treatment should be withdrawn before performing Octreoscan scintigraphy, though there are contradictory data (Dörr et al. 1993). The sensitivity for tumour detection is poor in patients with insulinomas (20-50%) (Krenning et al. 1993) in comparison with other endocrine tumours. However it was 80% in a series of 14 insulinoma patients with the use of SPECT (single-photon emission computed tomography) and an injected activity of 250 MBq of Octreoscan instead of the commonly recommended activity of 150-200 MBq (Schillaci et al. 2000). We only found a 24% sensitivity and neither pre-treatment with octreotide nor the lack of expression of sst2A receptors could account for all the negative scans (Vezzosi et al. 2005). In our experience, Octreoscan scintigraphy proved to be useful in a patient with an ectopic insulinoma, which was located about 2 cm below the body of the pancreas. Using the same technique for Octreoscan scintigraphy, 89.1% of non-insulinoma well-differentiated digestive endocrine tumours were detected in our centre. Small tumours cannot be detected by Octreoscan scintigraphy (Dromain et al. 2005). Octreoscan displays a lower affinity for sst2 receptors than octreotide (Reubi et al. 2000). Specific problems of imaging techniques may play a role in this low detection of insulinomas, even in sst2-positive insulinomas (Vezzosi et al. 2005). Octreoscan scintigraphy may help in localizing metastases, but MRI is better than Octreoscan scintigraphy for detection of liver metastases of endocrine tumours (Dromain et al. 2005). To date, the systematic use of Octreoscan scintigraphy in insulinoma patients is questionable.

Positron emission tomography (PET) with 18-F-labelled deoxy-glucose (FDG) has not proven advantageous for imaging endocrine tumours with the exception of poorly

differentiated, highly proliferative tumours (Pasquali et al. 1998; Sundin et al. 2009). The unstable glucose levels in insulinoma patients may also increase the difficulties.

Since pancreatic endocrine tumours are part of the APUDomas because of their ability for amine precursor uptake and decarboxylation through the action of aromatic amino acid decarboxylase, ¹⁸F-labelled-DOPA was also employed as a tracer. The first results in 10 patients with hyperinsulinemic hypoglycaemia were very encouraging. The pancreatic lesion was localized in 9/10 patients with subsequent confirmation by histological analysis (Kauhanen et al. 2007). The following studies did not confirm these results. A 27% sensitivity was reported for detection of pancreatic endocrine tumours (Montravers et al. 2009). In six patients with hyperinsulinemic hypoglycaemia (4 solitary insulinomas, 1 diffuse beta-cell hyperplasia, 1 malignant insulinoma), F-DOPA-PET was positive in only one case and it underestimated the extent of the disease in the malignant insulinoma with liver metastases (Tessonnier et al. 2010). More data are necessary to conclude, but to date F-DOPA PET does not appear to be a major help in managing pancreatic endocrine tumours.

The first results achieved with a radiolabelled GLP-1 analogue seem promising. Insulinomas were reported to be characterized by a very high incidence of GLP-1 receptors, these receptors being expressed in a particularly high density (Reubi & Waser 2003). A radiolabelled GLP-1 analogue (¹¹¹In-DOTA-exendin-4) was employed in 6 patients (5 with pancreatic insulinomas, 1 with an extrapancreatic insulinoma). Scintigraphy with GLP-1 analogue correctly localized the insulinoma in all 6 patients, while CT-scan was positive in 1, MRI-scan in 1 and endoscopic ultrasound in 4. Four patients had an intense uptake 4 hours after injection, and the other 2 patients showed demarcation between tumour and kidney only at late scans 3-7 days after injection (Christ et al. 2009). Interestingly, while exendin-4 does not induce hypoglycaemia in normal subjects, the insulinoma patients experienced a decrease in plasma glucose levels, with a nadir 40 min after injection, and an exogenous glucose infusion was necessary in 3 patients (for a maximum of 120 min), so that scintigraphy with radiolabelled exendin-4 appears to be also a provocative test in some insulinoma patients, and plasma glucose levels must be monitored after injection.

Finally trans-hepatic pancreatic venous sampling, to screen for an insulin concentration gradient, or calcium injection after selective catheterization of the arteries supplying the pancreas combined with measurement of insulin levels in the right hepatic vein can be used in difficult cases. The latter method was first described by Doppman et al (Doppman et al. 1993). A recent report by an expert team has evaluated the diagnostic accuracy of this technique (Guettier et al. 2009). A 2-fold or greater step-up in the right hepatic vein insulin concentration from baseline at times 20, 40 or 60 seconds after injection was considered to be positive. When a positive response was found at more than one injection site, the dominant site was used to predict tumour localization. In the absence of anatomical variants, a positive response to calcium injection in the gastroduodenal artery or superior mesenteric artery predicts a head-neck tumour, a positive response to the injection into the proximal splenic or the midsplenic artery predicts a body-tail tumour, and a response to calcium injection into the proper hepatic artery represents liver metastases. In 45 patients with surgically proven insulinomas, 38 (84%) localized to the correct region; in 5/45 (11%) the result was falsely negative, and 2/45 (4%) had false-positive localizations. Thus in expert hands selective intra-arterial calcium stimulation is a valuable tool to localize insulinomas when conventional imaging is negative. However, as pointed out by the expert group

(Guettier et al. 2009), there are several caveats, because this technique is based on the following 3 assumptions: 1) a 2-fold insulin increase is pathological; 2) normal beta cells do not show a positive response to calcium injection; 3) insulinomas always respond to calcium injection. All 3 assumptions can be challenged on the basis of the available data. According to Guettier's report, there was no explanation for 3 false-negative cases of insulinomas. A 2-fold increase in insulin levels was found in two or more vessels in 24 of 45 cases, which could suggest that some normal pancreatic areas respond to calcium injection, as already reported by Wiesli (Wiesli et al. 2004a), who recommended that only a 5-fold increase should be considered as a positive response if insulin levels are measured with an insulin-specific assay. This invasive test should probably be a last-line investigation in patients with hypoglycaemia related to endogenous hyperinsulinism that cannot be controlled easily by a medical treatment. Within the last 10 years, we used this method according to the modified protocol described by O'Shea (O'Shea et al. 1996) in only two patients, who were finally found to have nesidioblastosis (with two heterozygous mutations in the ABCC8 gene in one patient) with false positive "pseudo-insulinoma" results.

A recent study (Druce et al. 2010) compared the diagnostic accuracy of most methods employed to localize insulinomas in the years 1990-2009 in 36 patients, among whom 30 were treated by surgery. Among these 30 patients, 25 had CT and 28 had MRI with successful localization in 16 (64%) and 21 (75%) by CT and MRI, respectively. Together this led to 80% of successful localizations. Radiolabelled octreotide scanning was positive in 10 out of 20 cases (50%). Endoscopic ultrasound identified 17 tumours in 26 patients (65.4%). 27 patients had selective intra-arterial calcium stimulation: 6 (22%) did not localize, 17 (63%) were correctly localized, and 4 (15%) gave discordant or confusing results. Thus combination of CT and MRI predicts tumour localization with high accuracy, Octreoscan and endoscopic ultrasound are less helpful but could be valuable in selected cases, and calcium stimulation may provide an additional functional perspective.

In most patients, by now, multidetector CT-scan (with trans-abdominal ultrasound and/or MRI as complementary techniques) employed by an experienced radiologist will localize insulinomas, and must be considered as a first-line examination, while contrast-enhanced ultrasound needs further evaluation.

2.4 Treatment

2.4.1 Surgery

Surgery remains the only curative treatment of insulinomas. Long-term remission can be achieved by surgery in 95% of patients according to a recent study (Zhao et al. 2011). Two different types of surgery can be performed : minimal resection i.e. either tumour enucleation whenever it is possible or central pancreatectomy, or a more extended resection, i.e. left-sided pancreatectomy or pancreatico-duodenectomy. The type of surgery depends on the size and the location of the tumour and of its proximity with specific anatomical structures (pancreatic duct, vessels, adjacent organs). The improvement in the pre-operative imaging techniques enables the surgeon to have an accurate pre-operative topographic assessment and to decide the surgical approach pre-operatively. However intra-operative bidigital palpation and ultrasound remain valuable (Fendrich et al. 2009).

Whenever it is possible, tumour enucleation is to be chosen (Crippa et al. 2007). It allows to cure the patient in most cases with minimized risks of post-operative pancreatic exocrine deficiency and diabetes mellitus. It must be performed only to remove small tumours on the surface of the pancreas, with a distance of more than 2-3 mm between the

tumour and the pancreatic duct (Finlayson & Clark 2004). Providing that the tumour present with the above mentioned characteristics, and that surgery is performed by experienced surgeons, the risk of pancreatic fistula is not higher than that observed in larger resections of the pancreas (Kooby et al. 2008). When tumour enucleation is not possible, central pancreatectomy for a tumour in the pancreatic neck or adjacent body is preferred by several groups (Muller et al. 2006; Crippa et al. 2007; Zhao et al. 2011), in order to preserve a functional pancreatic gland, and to reduce the risks of post-operative pancreatic exocrine deficiency and diabetes mellitus (Crippa et al. 2007; Hirono et al. 2009). A larger pancreatic resection, i.e. left-sided pancreatectomy, ideally spleen-preserving, or pancreaticoduodenectomy, is preferred when the insulinoma is in close proximity to the pancreatic duct in order to lower the risk of pancreatic fistula (Carrere et al. 2007; Nikfarjam et al. 2008). If a plane between the tumour capsule and the pancreatic parenchyma cannot be easily identified, resection is indicated instead of enucleation (Fendrich et al. 2009). A large resection is also preferable for big invasive insulinomas that are suspected to be malignant.

When enucleation is possible, or even when left-sided pancreatectomy is to be performed, laparoscopy is now employed (Crippa et al. 2007). It reduces the duration of the stay in the hospital and improves the post-operative quality of life (Zhao et al. 2011). It must be performed only by experienced surgeons. It can be employed only if the insulinoma has been accurately localized preoperatively. It does not allow intra-operative bi-digital palpation of the pancreas. Laparoscopic ultrasound can be now performed in many expert centres and can localize the insulinoma and evaluate its proximity with the pancreatic duct and the possibility of performing tumour enucleation.

When no insulinoma was found intra-operatively, blind distal pancreatectomy had been recommended several years ago, but to date, such procedure must not be performed (Hirshberg et al. 2002), due to its short-term and long-term morbidity and its frequent failure to achieve a cure of the disease. If no insulinoma is found, it is recommended to stop the operation, then to perform new investigations in order to localize the insulinoma, including invasive techniques.

Morbidity and mortality depend on the type of surgery. Mortality is almost 0% for enucleation, but may reach 1-2% for left-sided pancreatectomy and up to 4-5% for pancreaticoduodenectomy. The most frequent short-term complication of pancreatic surgery is pancreatic fistula. Pancreatic fistulae are more frequent after enucleation or left-sided pancreatectomy, but their consequences are more severe after pancreaticoduodenectomy, due to infectious or haemorrhagic complications. They occur globally in 3-60% of cases, depending on the definition (Pannegeon et al. 2006; Yoshioka et al. 2010; Zhao et al. 2011). Most of them are asymptomatic and no additional treatment is necessary. The clinical prevalence of pancreatic fistulae is about 14% (Zhao et al. 2011). Other complications are intra-abdominal abscess (6.6%), pulmonary infections (3.7%), wound infection (2.5%), delayed gastric emptying (2.2%), abdominal bleeding (1.3%) acute pancreatitis (0.6%) and pulmonary embolism (0.6%) (Zhao et al. 2011). Long-term complications also depend on the type of surgery. Pancreatic exocrine deficiency and diabetes mellitus almost never occur after enucleation or central pancreatectomy. Pancreaticoduodenectomy results in exocrine pancreatic deficiency in 60% of cases, and left-sided pancreatectomy may lead to 5-10% diabetes mellitus. Therefore, limited pancreatic resection such as tumour enucleation or central pancreatectomy are preferred whenever they are technically possible.

2.4.2 Medical treatment

A medical treatment must be given to insulinoma patients in order to control the hypoglycaemia while the patient is awaiting surgery. A long-term medical treatment is given only if surgery is technically impossible or contra-indicated.

In some patients a medical treatment can result in controlling the hypoglycaemia. Evaluation of the occurrence of hypoglycaemia could probably be improved by continuous glucose monitoring (Munir et al. 2008). However sudden occurrence of severe hypoglycaemic spells cannot be ruled out, so that even if medications seem to be effective, surgery must not be delayed or cancelled when a surgical cure is possible. Dietary advice is useful but generally not sufficient to avoid hypoglycaemia. The patient must be advised regarding the symptoms suggesting hypoglycaemia, and what must be done when such symptoms occur. Self monitoring of glucose levels is recommended in order to detect asymptomatic episodes of hypoglycaemia and to prevent occurrence of hypoglycaemic spells, by treating asymptomatic abnormal lowering of glucose levels. The patients should be advised regarding everyday personal safety, to avoid possible consequences of dizziness and loss of consciousness.

Diazoxide (a benzothiazide) allows direct suppression of insulin secretion by beta cells through its effect on K-ATP channel. It stimulates hepatic gluconeogenesis and lowers glucose utilization by muscle cells (Altszuler et al. 1977). It can be given bid or tid at a total daily dose of 150-400 mg in most cases. It can control symptomatic hypoglycaemia in 50-60% of the patients (Stefanini et al. 1974). Adverse effects have been reported in about half of the patients. They comprise mainly fluid retention with oedemas, hypokalemia, digestive intolerance with nausea, cutaneous rashes and hirsutism. Diuretics may be added to treatment with diazoxide in order to control oedemas, and thiazides are known to potentiate the anti-hypoglycemic effects of diazoxide, but may induce electrolytic disorders or cause worsening of hypokalemia.

Somatostatin analogues can achieve normalization of plasma glucose levels in 50-60% of the patients (Vezzosi et al. 2008). There are only few adverse effects, mostly digestive intolerance with diarrhoea and steatorrhea. We did not observe a tachyphylaxis phenomenon when using somatostatin analogues in insulinoma patients. The dose of octreotide that was found to control the hypoglycaemia had to be determined on an individual basis, since the doses varied between 50 and 2000 µg per day. Somatostatin analogues inhibit insulin secretion mainly through their effects on sst2A and sst5 receptors, which were found in 70% of insulinomas (Bertherat et al. 2003). A short 100 µg octreotide test, not Octreoscan uptake, was predictive of the long-term efficacy of octreotide treatment on hypoglycaemia. This could be explained by the differing affinities of Octreoscan and octreotide for sst2 receptor (Reubi et al. 2000; Vezzosi et al. 2008). Worsening of hypoglycaemia after administration of somatostatin analogues has been reported (Healy et al. 2007). Such phenomenon could be explained by glucagon suppression by somatostatin analogues. It has not been observed in all series (Vezzosi et al. 2008).

Glucocorticoids may be used to normalize plasma glucose levels in insulinoma patients (Novotny et al. 2005). They decrease insulin secretion and increase peripheral insulin resistance. They are associated with several well-known adverse effects and they cannot be recommended as a first-line medication or for long-term use. Other medications have been employed with variable results, e.g. calcium channel blockers like verapamil (Stehouwer et al. 1989), and also phenytoin and propranolol. To date, m-TOR inhibitors have only been used in metastatic malignant insulinomas (see below).

3. Particular conditions

3.1 Malignant insulinomas

Malignant insulinomas represent 5-10% of insulinomas (Danforth et al. 1984; Service et al. 1991). The clinical and biological diagnostic criteria of insulinoma do not differ from those of benign insulinomas. On the other hand, there are specific issues in malignant insulinomas, regarding the diagnosis of malignancy, and the therapeutic management.

The histological diagnosis of malignancy is difficult. The only definite basis is the presence of a metastasis.

In clinical practice, a malignant insulinoma is generally a single large (> 4 cm) tumour. In most cases there are synchronous metastases, which allow to make the diagnosis of malignancy. The metastases are generally located in lymph nodes or in the liver. Thus careful radiological evaluation is valuable for the diagnosis of malignancy. Liver metastases of malignant insulinomas may present with a specific aspect on CT-scan (Atwell et al. 2008) and MRI (Sohn et al. 2001) with perilesional steatosis, due to a local effect of insulin. However metastases may be difficult to identify on CT-scan; a combination of pre-contrast, hepatic arterial-dominant phase and portal venous phase imaging improves the sensitivity for detection of liver metastases, since the lesion may be seen on only one of the three phases (Rockall & Reznick 2007), and large lesions may become necrotic and unenhanced by contrast agents. MRI, ultrasound and contrast-enhanced ultrasound may improve the detection of liver metastases. Typical liver metastases appear as low-signal intensity on T1 and high signal intensity on T2-weighted images, and are hypervascular on hepatic arterial dominant post-gadolinium images (Bader et al. 2001; Rockall & Reznick 2007). Nuclear imaging with Octreoscan can also be used, but false negative results are observed in small liver metastases, and MRI is better than Octreoscan scintigraphy for liver metastases detection (Dromain et al. 2005). However, Octreoscan uptake provides a tool to select patients for treatment with radio-labelled somatostatin analogues (Reubi et al. 2005). We did not confirm that Octreoscan uptake was predictive of the efficacy of somatostatin analogues on hypoglycaemia (Vezzosi et al. 2008; Maiza et al. 2011), unlike what had been previously shown in secreting endocrine tumours (Lamberts et al. 1990).

More rarely, the diagnosis of malignancy is suspected on the basis of the histo-pathological findings and it is confirmed later by occurrence of metastases. Apart from metastases and invasion of adjacent organs, suspicion of aggressive tumour behaviour is aroused by a tumour size > 2 cm, angioinvasion, and high proliferative activity (Kloppel 2007; Kloppel et al. 2009). A review of classification systems has been made by Klimstra et al (Klimstra et al. 2010).

The diagnosis of malignancy may be more difficult in some patients when the insulinoma has a benign presentation, even on the histo-pathological findings; in 48 operated insulinoma patients, with a median follow-up of 42 months, 2 patients initially diagnosed to have benign insulinomas were finally found to develop metastases (personal data). Therefore a prolonged follow-up is advisable. Since some patients with previous partial pancreatectomy may not fulfil the typical criteria for the diagnosis of insulinomas, recurrence of even mild clinical symptoms must not be neglected. Tumours of "uncertain behaviour" warrant a long-term clinical, biological and radiological follow-up. The follow-up of benign insulinomas after surgical remission is usually thought to be unnecessary (Arnold et al. 2009) but on the basis of our experience, we would recommend a clinical and biological follow-up and at least a radiological evaluation 1-2 years after surgery.

Regarding the treatment, malignant insulinomas can represent a double therapeutic challenge, i.e. that of the control of tumour progression, and the control of symptomatic

hypoglycaemia. Controlling the hypoglycaemia must not be neglected, since uncontrolled hypoglycaemia results in increased morbidity and mortality.

Regarding the tumour process, 10 year-survival is about 30% in patients with metastatic insulinomas (Service et al. 1976), with very heterogeneous courses. Some patients may present a very slow progression rate, even with a metastatic disease, and have long-term survival, whereas other patients present with rapid tumour progression and poor short-term survival rate. Predictive factors for rapid tumour progression remain to be established. They could be similar to those found for endocrine bronchial or digestive carcinomas, which comprise the presence of extra-hepatic metastases, the number of liver metastases, the proliferative index Ki67, the spontaneous progression of tumour volume in 3-6 months (Greenberg et al. 1987; Pape et al. 2004; Lepage et al. 2007). The anti-tumour strategy will not be detailed. Since malignant insulinomas are rare, there is no specific prospective study on this particular topic, so that the therapeutic strategy is similar to that of non secreting pancreatic endocrine carcinomas. Whenever it is possible, surgery must aim at totally removing the detectable lesions. However even in selected patients, post-operative complementary treatments are necessary, due to a frequent underestimation of liver metastases. In addition, even when total removal of the tumour has been performed with a R0-resection, recurrence is frequent (about 60% after a follow-up of 3 years) and the recurrence-free median survival is 5 years (Danforth et al. 1984). Treatments other than surgery combine local or regional treatments such as intra-arterial chemotherapy or chemoembolization of liver metastases (Roche et al. 2003) and radiofrequency (Berber et al. 2002), and systemic treatments such as radionuclide systemic administration (Ong et al. 2010), cytotoxic chemotherapy (traditional combination of streptozotocin, doxorubicin and 5-fluoro-uracil and more recently, capecitabine and temozolomide) (Moertel et al. 1992; Strosberg et al. 2008; Strosberg et al. 2011), or targeted therapies (Kulke et al. 2006; Dimou et al. 2010)(Raymond et al. 2011; Yao et al. 2011).

Symptomatic treatment of insulinomas aims at achieving short-term control of the hypoglycaemia while awaiting the effects of anti-tumour treatment or when anti-tumour treatments do not prove to be effective. Surgical removal of the tumour and its metastases is valuable in order to control the hypoglycaemia. Even a reduction of the tumour volume may result in reduction or transient subsiding of symptoms of hypoglycaemia (Sarmiento et al. 2002). A medical treatment is performed if there is no possible surgical cure, or as a complementary therapeutic approach. One should choose as first-line therapies medications that can achieve short-term control of hypoglycaemic spells, and do not jeopardize (by their possible adverse effects) the following use of other treatments. A few recent studies have addressed the issue of the control of severe hypoglycaemic spells in patients with inoperable malignant insulinomas (Bourcier et al. 2009; Ong et al. 2010; Maiza et al. 2011). All the medications used to treat hypoglycaemia in benign insulinomas can be employed, but in most cases, a combination of several hyperglycaemic medications is necessary (Vezzosi et al. 2008). Diazoxide or somatostatin analogues (2-3 subcutaneous injections daily, or long-acting forms, or continuous subcutaneous administration with a portable pump) may result in reduction or disappearance of hypoglycaemic spells in patients with metastatic insulinomas. Radiolabelled somatostatin analogues (especially the Lutetium labelled derivative of octreotide) may prove helpful in long-term control of hypoglycaemia and tumour progression in some patients (Ong et al. 2010). Calcium channel blockers like verapamil gave disappointing results (Stehouwer et al. 1989). Glucocorticoids were found to be effective on hypoglycaemia in malignant insulinomas, and some patients were improved even on doses as low as 2.5 mg of

prednisone per day (Novotny et al. 2005; Starke et al. 2005). m-TOR inhibitors seem now to be very promising regarding the control of the hypoglycaemia, in addition to their anti-tumour effects (Bourcier et al. 2009; Kulke et al. 2009). They can suppress insulin synthesis and secretion and increase insulin-resistance, thereby resulting in euglycaemia in patients with malignant insulinomas (Di Paolo et al. 2006). Chemoembolization of liver metastases can achieve the control of the hypoglycaemia (Moscetti et al. 2000). Repeated chemoembolization procedures are often necessary. Combining the use of continuous subcutaneous administration of a high dose of octreotide as a first-line treatment, followed if necessary by chemoembolization of liver metastases could achieve control of hypoglycaemic spells in a few inoperable patients (Maiza et al. 2011). Continuous glucose infusion may be necessary in some patients, while awaiting the efficacy of the other treatments. Vitamin B1 supplementation should be systematically implemented for patients with severe recurrent hypoglycaemia requiring large infusions of glucose, in order to prevent Wernicke's encephalopathy (Grunenwald et al. 2009).

3.2 Insulinomas as part of a genetic disorder

This section will be focused on 4 genetic disorders that are known to be responsible for pancreatic endocrine tumours in adult patients: multiple endocrine neoplasia 1 (MEN-1, OMIM # 131100), Von Hippel Lindau's disease (VHL, OMIM # 193300), tuberous sclerosis (TS) (a disease that is known to involve a dysregulation of the mTOR pathway) (TSC1 and TSC2 genes, OMIM # 191100 and # 191092), and neurofibromatosis type 1 (NF1, OMIM # 162200). Of these 4 disorders, MEN-1 is the most frequent cause of pancreatic endocrine tumours, particularly insulinomas, followed by order of decreasing frequency, by VHL, NF1 and TS (Jensen et al. 2008). It can be noticed that though pancreatic endocrine tumours are found in VHL patients, to our knowledge, there is no case report of a VHL patient with insulinoma. These 4 genetic disorders are caused by mutations in tumour-suppressor genes and are transmitted as autosomal dominant traits. Genetically-determined insulinoma does not differ from sporadic insulinoma regarding the clinical and biological diagnostic criteria. On the other hand, the therapeutic strategy may be different, particularly in MEN-1 insulinomas, since insulinomas are often multiple or associated with other secreting or non secreting endocrine tumours.

MEN-1 is related to a mutation in the *menin* gene, which maps to chromosome 11q13. Its prevalence is 1-10/100,000. The functional physiological role of *menin* has not yet been well established. *Menin* interacts with numerous proteins that play a role in transcriptional regulation, genomic stability, cell division and control of cell cycle (Balogh et al. 2006; Yang & Hua 2007). The major MEN-1 related endocrine disorders are pituitary adenomas, parathyroid adenomas or parathyroid hyperplasia, and secreting or non secreting pancreatic endocrine tumours. Regarding the secreting pancreatic endocrine tumours, the most frequent are gastrinomas (54%, 20-61% of patients) and insulinomas (18%, 7-31% of patients) (Jensen et al. 2008). MEN-1 related insulinomas occur generally in younger patients than sporadic insulinomas, with a greater prevalence in patients aged 25-35 years, but the age of occurrence is very different from patient to patient (5-80 years) (Cougard et al. 2000; Machens et al. 2007). Cystic pancreatic endocrine neoplasms could be more frequent in MEN-1 than in sporadic cases (Bordeianou et al. 2008).

The major characteristic of MEN-1 related insulinomas is that they are generally multiple tumours, so that diffuse microadenomatosis can be observed in the entire pancreatic gland, with multiple infracentimetric lesions of the pancreas (Anlauf et al. 2006). Often in such

cases there are also secreting or non secreting endocrine tumours that are more than 1 cm in size and are distributed in the whole pancreatic gland. Thus managing MEN-1-related insulinomas is often managing multiple pancreatic endocrine tumours, that may secrete insulin and other hormones (gastrinoma, glucagonoma...) or may be non secreting endocrine tumours (Cougard et al. 2000).

The natural course of endocrine disorders in MEN-1 patients was previously thought to start almost always by occurrence of primary hyperparathyroidism (Marx et al. 1998). However others have reported cases of MEN-1 revealed by a secreting pancreatic endocrine tumour; hyperparathyroidism had not been identified prior to the diagnosis of the secreting pancreatic tumour, because it had a mild or asymptomatic presentation (Thakker 2000). Thus insulinoma was the endocrine tumour that revealed MEN-1 in 14-30% of patients (O'Riordain et al. 1994; Cougard et al. 2000). Therefore, apparently sporadic insulinomas in young patients and multiple pancreatic lesions warrant to screen for MEN-1 even if there is no hyperparathyroidism.

The major issue is that of the treatment, since the multiple lesions increase the difficulty in achieving surgical cure of the disease. There is a mean of 3 pancreatic endocrine tumours (1 to 10) in the reported series of MEN-1 patients with pancreatic lesions who underwent surgery (Bartsch et al. 2005; Triponez et al. 2006). When managing an insulinoma patient with multiple pancreatic tumours, there could be several therapeutic strategies: 1. to perform total pancreatectomy with its associated morbidity and mortality rates; 2. to perform an extended resection of the pancreatic gland with enucleations of the tumours on the remaining pancreatic gland, which is also associated with significant morbidity and adds a risk of tumour recurrence. 3. to perform selective enucleations of the detected tumour(s), which increases the risk of re-operation for other tumours, and also may sometimes result in removing a non-secreting tumour, and not the insulin-secreting tumour if it has not been detected because of its smaller size; this could warrant a functional study of the lesions (with preoperative trans-hepatic venous sampling or arterial calcium injection, or intra-operative measurement of insulin) 4. to choose a medical therapeutic approach in responders who do not seem to have malignant lesions. In an operable insulinoma patient, curative surgery is generally attempted for the following two reasons. First, the prevalence of malignant insulinomas is similar in MEN-1 patients and in patients with sporadic insulinomas (Jensen et al. 2008). The prognosis of MEN-1 depends on the progression of malignant pancreatic endocrine tumours (Jensen et al. 2008). Second, in insulinoma patients, even in a patient who is thought to be controlled by a medical treatment, the sudden occurrence of severe symptomatic hypoglycaemia cannot be excluded, with its potentially serious and even fatal consequences. Therefore there is a general agreement regarding the necessity to perform surgery in MEN-1 patients with insulinomas. The extent of surgery remains debated. It mainly depends on the number and the location of the lesions, and the possibility to enucleate the lesion. One of the major advantages of preoperative endoscopic ultrasound could be in the evaluation of MEN-1 patients, since it can visualize even small lesions in the head of the pancreas (Proye et al. 2004). Left-sided pancreatectomy with enucleation of the tumours located in the pancreatic head is generally recommended in patients with MEN-1 related insulinomas, whenever it is possible (Cougard et al. 2000). Tumor enucleation gives acceptable results if the choice of the lowest morbidity rates is made. In those patients who present with a small number of pancreatic tumours, surgery may be less extensive and single or multiple tumour enucleation can be performed, when it is technically possible. The patient must be informed about the risk of recurrence and re-operation.

VHL disease is caused by a mutation in the VHL gene, which maps to chromosome 3p25. Its prevalence is 2 to 3/100,000. It is responsible for occurrence of renal cysts and cancers, hemangioblastomas in the central nervous system, pheochromocytomas and paragangliomas, and pancreatic tumours (Barontini & Dahia 2010). Pancreatic tumours and cysts are reported in 35-77% patients with VHL (Mukhopadhyay et al. 2002), but to date, to our knowledge, there is no case report of VHL-related insulinoma. The mean age of VHL patients who present with a pancreatic lesion varies between 29 and 38 years; unlike what is found MEN-1 patients with pancreatic endocrine tumours, 70% of VHL patients with pancreatic tumours have a single pancreatic tumour (Libutti et al. 2000; Blansfield et al. 2007). Pancreatic endocrine tumours represent only 9-17% of pancreatic lesions in VHL patients (Mukhopadhyay et al. 2002), most of them being non secreting tumours (Libutti et al. 2000). It has also been reported that pancreatic lesions in VHL patients were significantly associated with renal cancers. Since insulinomas are obviously rare in VHL, it seems reasonable to screen for VHL in an insulinoma patient only if the insulinoma is associated with other typical VHL lesions, particularly renal cancer.

Tuberous sclerosis is a phakomatosis characterized by cutaneous (facial angiofibromas also termed "adenoma sebaceum", hypomelanotic macules also termed "ash leaf spots", fibrous raised discoloured forehead plaques, and periungual fibromas), neurological (mental retardation, seizures, subependymal nodules and cortical/subcortical tubers), and ocular (hamartomas, also termed "phakomas") manifestations. The patients also present with renal cysts and angiomyolipomas and cardiac rhabdomyomas. TS is caused by mutations either in the TSC 1 gene (that encodes hamartin, and maps to chromosome 9q34) or in the TSC2 gene (that encodes tuberlin, and maps to chromosome 16p13.3) (Lodish & Stratakis 2010). Its prevalence is about 1/10,000 (Osborne et al. 1991). The occurrence of insulinomas in TS patients has been reported very rarely (Davoren & Epstein 1992; Kim et al. 1995; Boubaddi et al. 1997; Eledrisi et al. 2002; Dworakowska & Grossman 2009). It is generally found in patients with mutations in the TSC2 gene (Merritt et al. 2006). In all reported cases, the insulinoma was found in patients aged more than 20, many years after that the diagnosis of TS had been made. Thus insulinoma is never the first manifestation of TS. Consequently, there is no reason to screen for TS in insulinoma patients. On the other hand, in a patient who is known to have TS, the re-occurrence of neurological or psychiatric symptoms warrants measurement of plasma glucose concentration.

Neurofibromatosis type 1 (NF1) ("Von Recklinghausen's disease") is caused by a mutation in the NF1 gene which maps to chromosome 17q11.2 and encodes a protein named fibromin. The main clinical signs are cutaneous "café-au-lait" spots, neurofibromas, Lisch nodules on iris surface, optic gliomas and bone dysplasia. Its prevalence is 1 in 4000 to 5000. The most frequent endocrine tumour is pheochromocytoma. Pancreatic endocrine tumours are rare (0-10%). Digestive tumours in NF1 are gastrointestinal stromal tumours (GIST), and duodenal somatostatinomas that characteristically cause biliary dilatation (Miettinen et al. 2006). Insulinomas are exceptional in NF1 (Perren et al. 2006).

3.3 Nesidioblastosis

There is no general agreement regarding the definition of adult nesidioblastosis. Nesidioblastosis represents a state of diffuse beta cell hyperfunction (though not necessarily uniform in all cases), also termed "non-insulinoma persistent hyperinsulinemic hypoglycaemia (NIPHH)" (Christesen et al. 2008). Such patients have insulin-mediated hypoglycaemia, either in the fasting or in the postprandial state. It also comprises cases

reported as “non insulinoma pancreatogenic hypoglycaemia syndrome (NIPHS)”, i.e. patients who only suffer from reactive insulin-mediated hypoglycaemia, who have a negative fast test without definite pancreatic endocrine tumour, and without mutations in the ABCC8 and KCNJ11 genes (Service et al. 1999). Though rare, it is not quite exceptional among adult patients with hypoglycaemia related to endogenous hyperinsulinism: 4/128 (3%) patients (Raffel et al. 2007), 15/232 (6%) patients (Anlauf et al. 2005b), and even 5/32 (16%) patients (Witteles et al. 2001). We have made the diagnosis of idiopathic nesidioblastosis only in 4 patients for 20 years (1990-2010), while during the same 20 years 69 patients were diagnosed to have insulinomas in our institution; in addition, two other adult patients who had presented symptoms since the early childhood were found to have ABCC8 or glutamate dehydrogenase gene mutations.

Adult nesidioblastosis is likely to represent a heterogeneous disorder and whether it has specific histological correlates remains debated. The first histological reported features were islet cell enlargement, beta cells budding off ductular epithelium, and islets in apposition to ducts. Such aspects were found in an autopsy series in 36% of subjects without hypoglycaemia (Karnauchow PN 1981), whereas using morphometric criteria, patients with NIPHH could not be distinguished from controls (Goudswaard et al. 1984). In 15 adults with nesidioblastosis, blinded interobserver analysis showed beta-cell hypertrophy with enlarged and hyperchromatic nuclei; the interobserver analysis revealed 100% specificity and 87.7% sensitivity for these criteria (Anlauf et al. 2005b). The degree and extent of these features vary much more from patient to patient than in newborns (Kloppel et al. 2008). The interpretation of histological findings is not unequivocal, as shown by the divergent conclusions regarding 6 patients with reactive insulin-mediated hypoglycaemia after bypass surgery (Service et al. 2005; Meier et al. 2006). In addition, Meier et al. reported a positive correlation between beta cell nuclear diameter and body mass index, so that the actual meaning of an increased nuclear size in beta cells can be debated. In 4 operated patients who all had transient remission of hypoglycaemia for about one year after left-sided pancreatectomy, the histological conclusions were nesidioblastosis in 2 patients, micronodular islet cell hyperplasia in one case, and presence of some enlarged nuclei in rare pancreatic areas in one patient (who had two heterozygous mutations of the ABCC8 gene) (personal data).

Nesidioblastosis must not be confused with the recently identified pathological entity called insulinomatosis (Anlauf et al. 2009) which has been described in 14 patients, and is characterized by the synchronous and metachronous occurrence of insulinomas, multiple insulinoma precursor lesions, and rare development of metastases (all but one patient had benign disease), but common recurrent hypoglycaemia.

Nesidioblastosis may be related to well identified genetic disorders with mutations in genes that regulate beta cell insulin secretion (Flanagan et al. 2011a; Flanagan et al. 2011b; Palladino & Stanley 2011) (see above, differential diagnosis) and in such cases, it may occasionally be diagnosed in adult patients (Christesen et al. 2008). It has also been reported to be an adult-onset disease occurring in patients who had been previously treated by insulin, or a sulfonylurea, and in patients with MEN-1, Zollinger-Ellison and Werner-Morrison syndromes (Service et al. 1999). A higher rate of nesidioblastosis in MEN-1 adult patients has not been confirmed by all studies (Anlauf et al. 2005a). None of our patients with adult nesidioblastosis was found to have MEN-1. Conversion of insulin-dependent diabetes mellitus into nesidioblastosis has also been reported (Raffel et al. 2006). Recently, it has been found in patients after gastric bypass surgery (0.5-8 years after surgery in 5/6

patients) but whether such patients have actual structural pancreatic abnormalities is still debated (see differential diagnosis, dumping syndrome). Most reported patients with adult-onset nesidioblastosis do not have any particular medical history and do not present with mutations known to be associated with hypoglycaemia in young children.

The diagnosis of nesidioblastosis is made in patients with definite biological evidence of hypoglycaemia related to endogenous hyperinsulinism (as in insulinoma patients, see biological diagnosis) in the absence of insulin secretagogues, autoimmune hypoglycaemia, and detectable pancreatic tumour. There is neither clinical nor biological basis to make a distinction between insulinoma and nesidioblastosis. Patients with nesidioblastosis may have a positive fast test (as in all our patients), though patients with NIPHS have negative fast tests and only reactive insulin-mediated hypoglycaemia; on the other hand, very rare insulinoma patients may present with a negative fast test, and some of them have only reactive insulin-mediated hypoglycaemia. The diagnostic specificity of multi-site insulin stimulation by intra-arterial calcium injection is not fully established: such insulin stimulation after intra-arterial calcium injection was found in normal pancreatic areas for unknown reasons (Wiesli et al. 2004a; Guettier et al. 2009), and has been reported in patients with factitious hypoglycaemia related to insulin secretagogues (Hirshberg et al. 2001). In addition, intra-arterial calcium stimulation may provide a pseudo-insulinoma response pattern in patients with adult nesidioblastosis, maybe because nesidioblastosis is not evenly distributed in the pancreas. One must also be reminded that nesidioblastosis has been found in patients who had concurrent insulinoma (Bright et al. 2008) (Service et al. 1999). Slight focal pancreatic abnormalities have been reported with radionuclide imaging (Kauhanen et al. 2007).

The natural course of adult-onset nesidioblastosis is not well established. Most patients require a medical and/or surgical treatment. In an obese patient with idiopathic nesidioblastosis who had been treated by left-sided pancreatectomy and high doses of octreotide, hypoglycaemia finally subsided during the perimenopausal years, and changed to mild type-2 diabetes mellitus. No similar change was observed in other patients with nesidioblastosis, though the dose of diazoxide could be decreased in one patient during the perimenopausal years (unpublished personal data).

A medical treatment is the first-line therapeutic approach for nesidioblastosis, but it may not be sufficient to control the hypoglycaemia, and pancreatic surgery must often be performed. Diazoxide remains the reference medication for nesidioblastosis, and is often effective to control the hypoglycaemia, at least after partial pancreatectomy (Arao et al. 2006). Long-term treatment with somatostatin analogues has also been reported to be effective, without the side effects of diazoxide (Vezzosi et al. 2008). One of our patients was treated with continuous subcutaneous administration of a high dose of octreotide throughout her pregnancy, without any detectable maternal or foetal adverse effect (Boulanger et al. 2004). Calcium channel blockers have been employed (Witteles et al. 2001) (Vella & Service 2007). Pancreatic surgery, guided by the results of transhepatic venous sampling or those of insulin stimulation after selective intraarterial calcium injection, is often performed. The extent of surgery is controversial, in order to achieve a total control or a significant improvement of hypoglycaemia, without pancreatic insufficiency (Raffel et al. 2007). Selective intra-arterial calcium injection usually helps in choosing the extent of pancreatectomy (Toyomasu et al. 2009). Total pancreatectomy cannot be recommended, since complete or acceptable control of the hypoglycaemia can be achieved in most patients by partial pancreatectomy followed if necessary by a medical treatment. Spleen-preserving distal pancreatectomy is often performed unless the results suggest a proximal pancreatic

origin for excess insulin secretion (Starke et al. 2006). Four of our patients with nesidioblastosis were treated by left-sided pancreatectomy; all of them had transient remission of hypoglycaemia for about one year, then acceptable control was observed with diazoxide or octreotide, which proved to be more effective to control hypoglycaemia after partial pancreatectomy. 70%-distal pancreatectomy was performed in 5 patients with nesidioblastosis (Witteles et al. 2001) resulting in long-term remission in 3 patients, and some recurrences of hypoglycaemia in 2 patients, successfully treated by calcium channel blockers, with a follow-up of 1.5-21 years. Thus 60-75% resection of the pancreatic gland, guided by insulin venous gradient or insulin stimulation by selective intraarterial calcium injection, and followed if necessary by a medical therapy, appears to be a reasonable treatment for adult nesidioblastosis when enough efficacy cannot be achieved by medical therapy alone.

4. References

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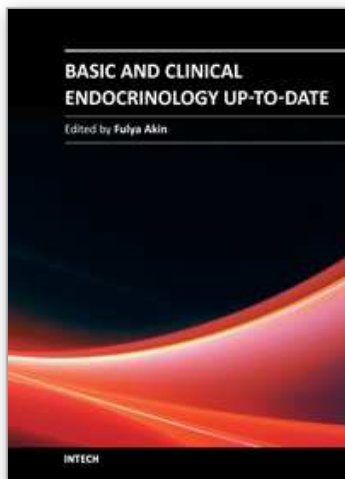
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51000 Rijeka, Croatia
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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