INTRODUCTION

An insulinoma is a neuroendocrine tumor, belonging to the neoplasia islet cells, deriving from pancreatic islet cells, which produce unregulated excessive amounts of insulin.

Under normal conditions, in a healthy person the insulin secretion increases after food ingestion. In the fasting state insulin secretion decreases when the blood glucose concentration falls. Insulin secretion stops when the blood glucose concentration falls to a value lower than about 60 mg/dl. This autoregulation is disturbed in case of an insulinoma, which produces and secretes insulin independent of the actual blood glucose concentration. The underlying defect of the islet cells in the tumor seems to be a diminished capacity to store insulin as one can see by electron microscopy.1

About more than half of neuroendocrine tumors are insulinomas, followed by gastrinomas, vasoactive intestinal polypeptide producing tumors (VIPomas) and glucagonomas.

About 85 to 90 per cent of insulinomas are benign, 10 to 15 per cent are malignant with metastases, mostly in the liver. In 1-2% of cases an ectopic localisation is found. About 5% of insulinomas are associated with MEN 1.

Of the 52 patients with insulinomas, which we
have observed during the last 30 years, in our own experience, 47 patients have had a benign tumor. Two patients have had a malignant tumor with liver metastases. In one patient a diffuse hyperplasia was found, and two times in children nesidioblastosis was diagnosed.2,3

The association between hypoglycaemia and β-cell tumors was first noted by Wilder in 1927.4 In 1935 Whipple5 described the triad of:
- dimming and disturbance of consciousness,
- abnormal low blood glucose concentrations,
- immediate relief by glucose injection,
as diagnostic criteria for insulin-producing islets cell tumors.

Today, this triad is completed by the determination of the insulin- and C-peptide concentration, and, additionally, by the determination of the proinsulin concentration or split products of proinsulin.6-8

**DIAGNOSIS**

The most important point for the diagnosis of an insulinoma is to take into consideration the possibility of a hypoglycaemia. In the majority of our cases hypoglycaemias were not recognised for a longer period of time. Very often patients described episodes of attacks lasting two to five years, sometimes with longer intervals between the several periods of, retrospectively, suspected hypoglycaemias. In one case attacks began 10 years before.2,3

**Definition of hypoglycaemia**

There are two definitions of hypoglycaemia:
- the biochemical: total blood glucose value lower than 45 mg/dl;
- the clinical: signs of neuroglycopenia, and signs of counter-regulatory catecholamine release.

**Differential diagnosis**

Hypoglycaemia can mimic an abundance of neurological or psychiatric symptoms.

In the beginning of the period of this 30-year-synopsis in about half of our patients an epileptic disorder was assumed, and sometimes patients were treated for a long time with antiepileptic drugs.

In the last decade the situation has changed. Now we see a lot of patients, admitted to our hospital, that are suspected with insulinoma. Most of these patients have had only signs of a neuro-psycho-vegetative lability, which were misinterpreted as hypoglycemic symptoms, or they have had a functional, reactive postprandial hypoglycaemia.

Himwich has given in 1951 a graded scale for the development of neuro-psychiatric symptoms in the course of falling blood glucose concentrations.9 (Table 1)

**Table 1.** Stepwise development of neuro-psychiatric symptoms in the course of hypoglycaemia (Adapted from Himwich9)

<table>
<thead>
<tr>
<th>Parasympathetic reactions:</th>
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<tbody>
<tr>
<td>Voracious appetite, nausea, vomiting, reduced muscle strengths</td>
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</table>

<table>
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<tr>
<th>Cortical phase:</th>
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</thead>
<tbody>
<tr>
<td>Reduced memory function, confusion, disorientation, agitation, psychomotor crisis, intermittent delirious states, aphasia, diplopia, reversible hemiplegia</td>
</tr>
</tbody>
</table>

**Symptoms of catecholamine secretion:**
- Tremor, perspiration, tachycardia, blood pressure increase, hyperventilation, restlessness
- Subcortical phase: Somnolence, stupor, unconsciousness
- Mesencephal phase: Coma with general cerebral convulsive attacks
- Pontine phase: Irreversible brain damage
- Medullar phase: Decerebration, spinal automatism, exitus.

In our experience there is not such a clear cut graded behaviour.

**Differential diagnosis of hypoglycaemia from the clinical point of view**

It is convenient to divide hypoglycaemia according to the pathogenetic point of view. Thus, hypoglycaemia can be classified in exogenous and so-called endogenous.

Exogenous hypoglycaemias, e.g., in diabetic patients, over-treated with β-cytotropic compounds or with insulin, are not the theme of this article.

Endogenous hypoglycaemias can be divided in functional or organic hypoglycaemia.

From a clinical point of view it is more convenient to differentiate between hypoglycaemias in the fasting state and hypoglycaemias after food ingestion. (Table 2)

**Table 2.** Differential diagnosis of hypoglycaemia to exclude or to confirm the suspicious of insulinoma

<table>
<thead>
<tr>
<th>Hypoglycaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>After food ingestion</td>
</tr>
<tr>
<td>Functional or reactive</td>
</tr>
<tr>
<td>Vegetative lability</td>
</tr>
<tr>
<td>Dumping syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In the fasting state</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related to special disorders</td>
</tr>
<tr>
<td>Liver disease</td>
</tr>
<tr>
<td>M. Addison</td>
</tr>
<tr>
<td>Cachexia</td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
</tr>
<tr>
<td>Retropertioneal fibrosarcoma</td>
</tr>
<tr>
<td>Not related to special disorders</td>
</tr>
<tr>
<td>Insulinoma is suspected</td>
</tr>
</tbody>
</table>

**DIAGNOSTIC TOOLS**

If it is not possible to associate a fasting hypoglycaemia with other disturbances one should suspect an insulinoma!

Only in patients with insulinomas the constellation
of lowered fasting blood glucose levels and elevated insulin concentrations exist!

The most important diagnostic tool during clinical signs of hypoglycaemia is to draw a blood sample for the determination of the glucose and the insulin and C-peptide concentration, and proinsulin additively.

First: One should try to pick up a spontaneous hypoglycaemia according to Whipple's triad.

Second: Sometimes one waits for a spontaneous attack without success. Therefore it is helpful to draw blood specimens every morning after an overnight fast to look for the relationship between the glucose- and insulin-concentration. Often one may observe relative low blood glucose and relative high insulin levels.

Third: One can prolong the overnight fast for 36 hours until the next morning to provoke the situation of low blood glucose and high insulin level, or to provoke, indeed, a real hypoglycaemic attack. In textbooks fasting periods of 72 hours are recommended. But in our own experience the longest time until an attack, which made it necessary to stop the fasting test by carbohydrate application, was 18 hours. Therefore we decided to shorten the fasting time from 72 to 36 hour.

Index calculation
In the course of prolonged fasting the blood glucose concentration may fall to values a little lower than 55 mg/dl. Then it may be helpful to calculate the insulin/glucose ratio, a parameter, which is favoured in the literature indicating inappropriate β-cell secretion. In our own experience seldom patients without an insulinoma have had ratios above 0.25.

To improve specificity, the "Amended" Insulin to Glucose Ratio (AIGR) is more widely utilized and is calculated as:

\[
\text{AIGR} = \frac{\text{insulin (µu/mL) x 100}}{\text{glucose (mg/dL) - 30}}
\]

Normal individuals have an AIGR less than 50.

Suppression tests
The next steps in the diagnostic procedure are suppression tests. Normally the β-cell secretion will cease, when the blood glucose concentration falls below 60 mg/dl. To suppress the β-cell secretion the blood glucose level can be lowered artificially with exogenous insulin (0.1 IU/kg bodyweight of regular insulin i.v.).

The C-peptide concentration will fall more pronounced in healthy persons than in patients with insulinomas. According to Saddig this test can become more sensitive by special mathematical procedures, to avoid misinterpretations.

Another kind of suppression can be performed by somatostatin infusion. In healthy persons the insulin secretion stops, in islets cell autonomy secretion continues. We have not done somatostatin suppression tests in insulinomas in our clinic; therefore we have no personal experience with it.

Stimulation tests
Other diagnostic procedures are stimulation tests, e.g., the i.v. calcium infusion test (6 mg/kg b.w. /h). Normally the β-cell secretion will not change during calcium infusion; in insulinomas an increase is seen. In our hands only in 2 of 4 cases a clear cut increase was seen.

Other stimulation tests like the tolbutamide test, the glucagon test and the leucin test are obsolete today.

Oral glucose tolerance test (OGTT)
In contrast to other groups we do not favour the oral glucose tolerance test because a hypoglycaemia, e.g., three to five hours after glucose ingestion, could be a reactive or functional, but also an organic hypoglycaemia.

LOCALIZING PROCEDURES

When an autonomous hyperinsulinism by biochemical measurements is free of doubt, tumor localising procedures follow.

In Table 3 several procedures are listed.

Table 3. Tumor localising procedures

<table>
<thead>
<tr>
<th>Procedure</th>
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<tbody>
<tr>
<td><strong>Not Invasive</strong></td>
</tr>
<tr>
<td>Abdominal sonography</td>
</tr>
<tr>
<td>Endosonography</td>
</tr>
<tr>
<td>Computer tomography</td>
</tr>
<tr>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>(Scintigraphic procedures - 75seleno-methionin: obsolete)</td>
</tr>
<tr>
<td><strong>Invasive</strong></td>
</tr>
<tr>
<td>Arteriography of a. coeliaca and a. mesenterica cranialis</td>
</tr>
<tr>
<td>(ERCP: obsolete)</td>
</tr>
<tr>
<td>(PTC with superselective pancreatic venous blood sampling for insulin measurements: obsolete)</td>
</tr>
<tr>
<td><strong>Intraoperative</strong></td>
</tr>
<tr>
<td>Direct sonography of the pancreas</td>
</tr>
<tr>
<td>Venous blood sampling for measurements of insulin with an ultra rapid assay</td>
</tr>
<tr>
<td>Clamping procedures: BIOSTATOR</td>
</tr>
<tr>
<td>(Toluidine blue staining: obsolete)</td>
</tr>
</tbody>
</table>

Before computer tomography and magnetic resonance tomography became available, the simultaneous arteriography of the a. mesenterica cranialis and the a. coeliaca according to Boijsen was the most important method, successful in our hands in about 60% of the cases. Today the
endosonographic procedure seems to be the method of choice, as a non-invasive method with a high detection rate.

If intraoperative the tumor is not palpable (benign tumors have a diameter seldom more than 2 cm), intraoperative direct sonography of the pancreas is helpful. Also intraoperative direct stepwise venous sampling of blood for measurement of the insulin concentration with an ultra rapid working assay may be helpful.

**PITFALLS**

If hypoglycaemic attacks take place in a very dramatically scenery with impressive publicity be aware of hypoglycaemia factitia! In case of a self administration of insulin the concentration of insulin will be - sometimes extremely - elevated. The C-peptide concentration because of the suppression of the endogenous β-cell secretion will be very low. More difficult to discover is a self administration of β-cytotropic drugs as in these cases the C-peptide concentration is also elevated. Here it is necessary to perform drug analysis in urine samples to convict the patient.

**PREOPERATIVE TREATMENT**

When the diagnosis of autonomous hypersecretion of insulin with hypoglycaemic attacks is established, a preoperative treatment with diazoxide\(^{18,19}\) should be performed (300 - 450 mg for 5 - 10 days).

Diazoxide is a thiazide derivate which hampers the insulin secretion reversibly. In benign tumors a normalisation of glucose values can be reached. Unfortunately the side-effects like gastrointestinal irritability, fall of blood pressure with tachycardia, salt retention with oedema, and hirsutism does not allow generally a prolonged treatment to avoid an operation. Therefore after one to two weeks of treatment the patient should be operated.

**CONCLUSIONS**

A lot of procedures allow to diagnose the autonomous secretion or at least inadequate islets cell function in insulinoma patients.

But the most important point of all and the first step of diagnostic procedures is to guess neuroglycopenia. Therefore it is necessary to perform blood glucose determinations in every case of intermittent symptoms of a "brain dysfunction", to avoid misinterpretations, as a neuroglycopenia can mimic the whole spectrum of neurological or psychiatric disturbances.

**REFERENCES**