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Islet Hyperplasia in Adults: Challenge to Preoperatively Diagnose Non-Insulinoma Pancreatogenic Hypoglycemia Syndrome

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Abstract

Background: Pancreatic hyperfunctional islet hyperplasia in adults has been more and more frequently described in the literature. Postprandial neuroglycopenia, a negative normal fasting test, negative pancreatic imaging results, and positive intra-arterial calcium stimulation of serum insulin are characteristic. In affected patients the term non-insulinoma pancreatogenic hypoglycemia syndrome (NIPHS) was proposed.

Materials and Methods/Patients: We also encountered fasting hypoglycemia in such patients and therefore evaluated clinical and biochemical data in patients with NIPHS (n = 11), patients with insulinoma (n = 70), and patients in whom hypoglycemia was ruled out (n = 70).

Results: Patients with NIPHS were younger (median age: 41 years; range: 18–66) and mostly non-obese (median body mass index/BMI: 22.2 kg/m^2; range: 19–39) compared with patients with an insulinoma (median age: 50 years; median: BMI 26.1 kg/m^2). During an oral glucose tolerance test (OGTT) followed by a standard fasting test, neuroglycopenia was observed postprandially with a mean minimal blood glucose level of 36 ± 9 mg/dl in 7 out of 11 patients. Spontaneous hypoglycemia during the fast was 38 ± 5 mg/dl in 8 out of 11 patients. The corresponding insulin levels were 9.2 ± 9.8 mU/l (OGTT) and 6.8 ± 5.4 mU/l (fasting), significantly lower than in patients with insulinoma ($P < 0.001$), but not different from patients without hypoglycemia ($P = 0.05$). After pancreatic resection 8 patients (73%) were cured with enduring euglycemia. Pathohistological islet abnormalities with hyperplasia, hypertrophy, and microadenomatosis were confirmed in all patients.

Conclusion: In patients with postprandial and/or fasting neuroglycopenia NIPHS may be suspected when insulin levels are low but inadequately suppressed and localization studies failed to show a distinct pancreatic tumor.

Abbreviations: MEN-1: Multiple endocrine neoplasia type 1; NIPHS: Non-insulinoma pancreatogenic hypoglycemia syndrome; PHHI: Persistent hyperinsulinemic hypoglycemia of infancy; *SUR1* gene: Sulfonylurea receptor-1 gene; *Kir6.2* gene Potassium inward rectifier 6.2 gene

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INTRODUCTION

Surgical cure of endogenous hyperinsulinemic hypoglycemia, which is mostly attributed to benign insulin

secreting adenomas, reaches almost 100% in experienced hands.[1–3] Success may be jeopardized, however, in patients with malignant metastatic insulinoma, in patients with multiple adenomatous lesions in as yet unknown multiple endocrine neoplasia type 1 (MEN-1) disease, and in patients with diffuse islet cell hyperplasia.[4] While a MEN-1 syndrome can be diagnosed by family history and Menin gene analysis in most patients,[5–7] preoperative differentiation between patients with endogenous hyperinsulinism due to an insulinoma or rarely to islet hyperplasia/nesidioblastosis has been thought to be impossible by most authors.[8–10] Recently, Service *et al.*[11–13] described patients characterized predominantly by postprandial neuroglycopenia and a normal negative 72-hour fasting test, and proposed the term non-insulinoma pancreatogenic hypoglycemia syndrome (NIPHS). Since these patients may reflect a subset of a more heterogeneous group of patients with NIPHS, we questioned whether clinical data including patient history, localization studies, and hormone analysis from the oral glucose tolerance test (OGTT) and the fasting test may point toward NIPHS. With increasing experience from 11 patients operated on between 1994 and 2005, we accumulated data that enabled us to predict or at least suspect NIPHS preoperatively by means of rather characteristic blood glucose and serum insulin patterns obtained from a combined OGTT and standard supervised fasting test.

PATIENTS AND METHODS

During the three decades since 1975 we have diagnosed and surgically treated a total of 102 patients with classical benign insulinoma, median age 50 years (range: 15–81), median body mass index (BMI) 26.1 kg/m^2 (range: 16–38 kg/m^2), median HbA1c (n = 52) at admission 4.5% (range: 2.9%–6.2%). In addition, with the first patient seen in 1994, no insulinoma was found during surgery or seemed to be unlikely in a total of 11 patients. These mostly female patients (2 men and 9 women) suffered from not only postprandial hypoglycemia (7 out of 11 patients) but also fasting hypoglycemia (8 out of 11 patients). All patients reported clinical evidence of repeated neuroglycopenia obvious as impaired consciousness, mental function, and speech, and occasionally hemiparesis, but never seizures as often seen in patients with insulinoma. The basic clinical characteristics and relevant biochemical results of functional tests are summarized in Table 1. These 11 patients were younger (median age 41 years, range: 18–66 years), mostly nonobese (median BMI: 22.2 kg/m^2; range 19–39 kg/m^2), and presented with a higher basal HbA1c level (median 5.2%, range 4.0–5.7%), compared with the patients with insulinoma. The biochemical data of a 6-hour OGTT and a standard supervised fasting test for up to 72 hours were compared with available complete data sets from 70 patients with a proven benign insulinoma and 70 patients in whom a diagnosis of hypoglycemia could not be made (no hypoglycemia, Table 2).

OGTT and Supervised Fasting Test

Conventionally, in our institution the OGTT consisted of 100 g of glucose, which was replaced by 75 g in 2001, and was usually administered immediately preceding the fast. Blood samples drawn from an intravenous line kept patent by infusion of 0.9% saline were analyzed for venous blood glucose, serum insulin, c-peptide, and as of 2001 for proinsulin. Blood glucose was measured immediately by means of validated glucose analyzers based upon the glucose oxidase method (Beckman Instruments, Fullerton, CA, USA) or later the glucose dehydrogenase method (HemoCue, Aengelholm, Sweden). Sampling intervals were 30 minutes for the first 3 hours and hourly thereafter. After 6 hours the intervals were extended to 4 hours until completion of the fast within 72 hours (patients with no hypoglycemia) or until at least three consecutive and reproducible blood glucose values below 40 mg/dl were drawn within 15–30 minutes. Biochemical hypoglycemia was defined as any venous blood glucose below 40 mg/dl irrespective of clinical symptoms and clinically relevant hypoglycemia was defined as glycemia below 45 mg/dl in the presence of simultaneous symptoms. All tests were meticulously supervised by one of us (A.S.).

Hormone Assays

Commercially available assays were used for the analysis of serum insulin, c-peptide, and proinsulin. Due to recent advances in assay technology the insulin radioimmunoassay (Phadebas, Uppsala, Sweden; proinsulin cross-reaction 40%) had been replaced by an enzyme linked immunosorbent assay (iso-insulin ELISA; Mercodia, Uppsala, Sweden; proinsulin cross-reaction 54%) and as of 2001 by a specific electro-chemoluminescence immunoassay (ECLIA) run on a modular immunoanalyzer E170 (Elecsys Insulin; Roche Diagnostics, Mannheim, Germany; proinsulin cross-reaction ~0%). This resulted in lower limits of the insulin concentration being considered as completely suppressed levels and called for the necessity of separate proinsulin

Table 1.
Characteristics and biochemical test results of 11 patients with non-insulinoma pancreatogenic hypoglycemia syndrome

Number of patients	Year	Sex	Age (years)	BMI (kg/m^2)	HbA1c (%)	Oral glucose tolerance test						Standard supervised fasting test					
						BG min (mg/dl)	Time pp (min)	Insulin (mU/l)	I/G-ratio	c-Pept (ng/ml)	Proins (pmol/l)	BG min (mg/dl)	Time (hour)	Insulin (mU/l)	I/G-ratio	c-Pept (ng/ml)	Proins (pmol/l)
11	2005	Female	29	27.7	5.4	37	180	23.5	0.635	5.2	57	46	53	5.0	0.109	2.2	8
10	2004	Female	41	19.7	5.7	38	360	1.6	0.042	1.1	30	37	24	3.2	0.086	1.4	54
9	2004	Female	41	20.6	4.9	29	240	7.1	0.245	2.6	35	35	30	3.2	0.091	0.8	22
8	2004	Female	45	39.4	4.6	33	240	3.8	0.115	2.6	28	48	33	3.0	0.063	1.1	4
7	2003	Female	45	19.1	4.9	34	220	5.2	0.153	3.5	–	–	–	–	–	–	–
6	2002	Female	66	25.7	4.0	–	–	–	–	–	–	31	12	17.8	0.574	4.1	–
5	2001	Female	43	22.1	–	23	360	3.2	0.139	1.6	11	37	9	4.3	0.116	0.7	6
4	2001	Female	34	23.5	5.3	53	300	3.0	0.057	1.5	14	37	48	2.8	0.076	1.0	3
3	1998	Female	30	22.2	5.3	–	–	–	–	–	–	35	12	14.0	0.400	3.9	–
2	1996	Male	57	24.0	–	43	120	26.0	0.605	–	–	35	32	4.0	0.114	2.4	–
1	1994	Male	18	21.7	5.2	–	–	–	–	–	–	35	33	10.5	0.300	–	–
Mean			40.8	24.2	5.0	36.3	253	9.2	0.249	2.6	29.0	37.6	29	6.8	0.193	2.0	16.2
SD			13.3	5.7	0.5	9.1	84	9.8	0.237	1.4	16.6	5.3	15	5.4	0.174	1.3	19.8
Median			41.0	22.2	5.2	35.5	240	4.5	0.146	2.6	29.0	36.0	31	4.2	0.111	1.4	7.0
Range			18–66	19–39	4.0–5.7	23–53	120–360	2–26	0.04–0.6	1.1–5.2	11–57	31–48	9–53	3–18	0.06–0.6	0.7–4.1	3–54

BMI: body mass index; BG min: minimal blood glucose concentration; time pp (min): time in minutes elapsed postprandially; I/G-ratio: insulin-glucose ratio; c-pept: c-peptide; proins: proinsulin.

assays.[14] Intact proinsulin was measured by an immunoluminometric assay (ILMA)[15] without cross-reaction for insulin.

Pathology and Immunohistochemistry

Resected tissue specimens were dissected into 1-mm slices and carefully searched for visible or palpable tumors to confirm the absence of insulinoma. Tissue samples were taken at regular intervals of 5–10 mm, fixed in 4% buffered formalin and embedded in paraffin. Distribution, size, and variability of pancreatic islets were evaluated in hematoxylin- and eosin-stained slices. Immunohistochemical staining was performed with insulin antibodies diluted 1:100 (DAKO Diagnostica, Hamburg, Germany) and visualization of the antigen–antibody binding by means of the peroxidase method.

Statistical Analysis

Data in the text and tables are given as median and range (min–max) and mean ± SD (standard deviation). Any *P* values were calculated from unpaired two-sided *t*-tests using heterogeneous variances by means of Microsoft-Excel functions.

RESULTS

Six-Hour OGTT

As seen in Table 1, 3 patients (#1, 3, and 6) did not undergo an initial OGTT since available data during fasting hypoglycemia pointed clearly toward inadequately elevated insulin levels within the range of 10.5–17.8 mU/l and thus were suspected of suffering from insulinoma. Patient #2 presented with hyperinsulinemic postprandial hypoglycemia and fasting hypoglycemia after 32 hours with an elevated c-peptide concentration. Patients showed either postprandial hypoglycemia (n = 7) after 2–6 hours or fasting hypoglycemia after 9–48 hours (n = 8), or both (n = 3). Six patients (#2, 5, and 8–11) were able to efficiently counter-regulate the symptomatic and biochemical hypoglycemia back to normal blood glucose levels and hence later developed secondary fasting hypoglycemia or had a normal negative fasting test (n = 2). Only in patient #7 did the glucose-loading test have to be terminated prematurely after 4 hours due to the development of neuroglycopenia-induced hemiparesis.

Table 2.
Blood glucose (BG) and serum insulin concentrations during 6-hour oral glucose tolerance test (OGTT) and standard fasting test in patients with islet hyperplasia, patients with insulinoma, and patients without hypoglycemia

	Hyperplasia	Insulinoma	No hypoglycemia
6-hour OGTT	n = 8	n = 70	n = 70
BG min (mg/dl)	36 ± 9	46 ± 20	58 ± 11
		$P = 0.038$	$P = 0.0001$
Insulin at BG minimum (mU/l)	9.2 ± 9.8	28.7 ± 27.1	9.9 ± 8.2
		$P = 0.0004$	$P = 0.84$
Insulin/glucose ratio	0.249 ± 0.238	0.700 ± 0.670	0.179 ± 0.163
		$P = 0.0007$	$P = 0.44$
BG maximum (mg/dl)	165 ± 44	155 ± 50	151 ± 31
		$P = 0.59$	$P = 0.43$
Insulin maximum (mU/l)	105 ± 57	128 ± 94	113 ± 69
		$P = 0.34$	$P = 0.72$
Fasting test	n = 10	n = 70	n = 70
BG minimum (mg/dl)	38 ± 5	31 ± 7	47 ± 8
		$P = 0.004$	$P = 0.0002$
Insulin at BG minimum (mU/l)	6.8 ± 5.4	29.0 ± 26.9	2.9 ± 1.1
		$P < 0.0001$	$P = 0.048$
Insulin/glucose ratio	0.193 ± 0.174	0.977 ± 0.840	0.063 ± 0.024
		$P < 0.0001$	$P = 0.042$

Data are given as mean ± SD; *P* values are obtained from two-sided unpaired *t*-test assuming heterogeneous variances.

The insulin levels not only during the postprandial glucose nadir (BG min) but also during the fasting glucose nadir were clearly less than 4 mU/l in the majority of patients (4 and 5 patients respectively) and in contrast to mostly elevated proinsulin levels (11–57 pmol/l) during postprandial hypoglycemia (Table 1). C-peptide levels were never suppressed below the minimally recorded level of 0.7 ng/ml (patient #5) at any glucose nadir in any patient. The mean BG minimum and the corresponding serum insulin concentration as well as the resulting insulin/glucose ratios are summarized in Table 2 in a comparison of 70 patients with insulinoma and 70 without hypoglycemia. Postprandial hypoglycemia (mean 36 ± 9 mg/dl), evident in 7 out of 11 patients with islet hyperplasia, was rarely seen in patients with insulinoma (46 ± 20 mg/dl, $P = 0.038$), except for a few patients who did not tolerate fasting for more than a few hours, even after an initial oral glucose load. The group of patients shown to be non-hypoglycemic demonstrated significantly higher postprandial glucose nadirs (58 ± 11 mg/dl, $P = 0.0001$). Insulin levels at the glucose nadir in patients with islet hyperplasia, however, were similarly within the range of non-hypoglycemic patients (9.2 ± 9.8 vs. 9.9 ± 8.2 mU/l, $P = 0.84$), but clearly inadequately elevated for the degree of prevailing glycemia. The insulin/glucose ratio was significantly higher ($P = 0.0007$) in patients with insulinoma due to far higher insulin levels at the glucose nadir, but clearly does not seem to be a valuable discriminator among any of the patient groups due to large variations and overlap.

Despite statistically non-significant differences among the patient groups with regard to maximal glucose concentrations and maximal insulin concentrations after oral glucose loadings, the patients with islet hyperplasia did not show any evidence of clear-cut early postprandial hyperinsulinemia (insulin maximum 105 ± 57 mU/l), which could potentially be accountable for subsequent postprandial hypoglycemia.

Fasting Test

Clearly, differences among the three groups of patients emerge from the analysis of the fasting test data (Table 2). The glucose nadir was significantly lower in the patients with insulinoma (31 ± 7 mg/dl, $P = 0.004$), but significantly higher and within the normal range in patients without hypoglycemia (47 ± 8 mg/dl, $P = 0.0002$) compared with the patients with islet hyperplasia (38 ± 5 mg/dl). The concomitant insulin levels at the glucose nadir were significantly higher in patients with insulinoma (28.7 ± 27.1 mU/l, $P < 0.0001$), whereas patients without hypoglycemia presented with typically complete suppression of serum insulin (2.9 ± 1.1 mU/l) being barely significant compared with patients with islet hyperplasia (6.8 ± 5.4 mU/l, $P = 0.048$). Six out of 11 patients with islet hyperplasia presented with insulin levels of 4.3 mU/l and below despite biochemical hypogly-

Table 3.
Surgical procedures (resections) and descriptive histological results in patients with islet hyperplasia

Patient	Surgical procedure (resection size in cm)	Pathohistological (HE stains and anti-insulin immunohistochemistry)
11	Extended pancreatic head resection (head 7.2 × 4.3 × 2.3; body 4.2 × 3.3 × 1.8)	Polymorph irregular islets with ductuloinsular proliferations
10	Left resection of pancreatic tail (6.0 × 4.0 × 2.0)	Polycyclic trabecular islet complexes with three non-encapsulated microadenomas sized 2–6 mm (Fig. 1D)
9	Extended three-quarters left resection (19.5 × 3.3 × 1.3)	Polymorph hypertrophic + hyperplastic islets with ductuloinsular complexes (Fig. 1B)
8	Extended pancreatic left resection (15.3 × 4.8 × 2.7)	Irregular polymorph hyperplastic and hypertrophic islets with few ductuloinsular complexes
7	Pancreatic left resection (tail) (9.7 × 4.8 × 2.2)	Polymorph hyperplastic islets, dispersed small endocrine cell clusters, partially in peripancreatic fat, one microadenoma sized ~1 mm; (Fig. 1C)
6	Pancreatic head resection (head 6.2 × 4.3 × 1.3; body 4.3 × 2.3 × 1.8)	Trabecular islet-like endocrine cell clusters with fibrosis, nodular microadenoma in uncinate lobe sized < 2 mm
5	Pancreatic left resection (tail) (5.6 × 5.5 × 2.3)	Irregular polymorph islets, endocrine islet cell clusters in peripancreatic fat, fibrotic islet-like proliferation sized ~1 mm; (Fig. 1A)
4	Pancreatic left resection (tail) (7.2 × 4.8 × 1.8)	Irregular hyperplastic islets and islet-like cell clusters up to 220 μm, ductuloinsular proliferations
3	Extended pancreatic left resection (10 × 4.5 × 1.5)	Multifocal hyperplastic and hypertrophic islets, small endocrine cell clusters, periductular proliferations
2	Pancreatic left resection (tail) (5.5 × 4.0 × 2.2)	Islet and beta cell hypertrophy, nuclear hypertrophy
1	Pancreatic left resection (tail) (4.5 × 2.0 × 1.0)	Irregular polymorph islet hyperplasia and hypertrophy

cemia; proinsulin levels were increased in only 2 patients (22–54 pmol/l).

Imaging Results

Available and performed imaging, mostly endosonography, computed tomography, nuclear magnetic resonance tomography, and arterial angiography were negative in 5 patients and produced falsely positive results in 6 patients. The results proved to be confusing or misleading for the planned surgical strategy rather than clarifying the individual situation.

Selective Arterial Calcium Stimulation with Venous Sampling

In 2 patients (#8, #11) an intra-arterial calcium injection test with blood sampling from the right hepatic vein was performed as originally described by Doppman *et al.*[16]. A dose of 0.01–0.025 mval Ca/kg body weight was injected into selected arteries; a reduced dose was chosen for the grossly obese patient (#8). A positive 2- to 4-fold gradient of insulin concentrations within 30–60 seconds of injection was seen in the splenic artery (patient #8; 17.6 mU/l vs. 41.1 mU/l) or in the upper mesenteric artery (patient #11; 18 mU/l vs. 63 mU/l), clearly enforcing the surgical strategy. In both patients, who had normal negative fasting tests, the results helped to discriminate in favor of pathological insulin secretion.

Surgical Procedures and Histology

Table 3 summarizes the individual surgical resections after careful exploration and total exposure of the entire pancreatic organ. The pancreas was gently palpated bidigitally and scanned by intraoperative ultrasonography (IOUS). Only after excluding single or multiple pancreatic tumors a normal left-sided (left of the mesenteric vein) or extended left-sided (right side of mesenteric vein and pancreatic neck) up to subtotal pancreatic resection (with resection of the uncinate lobe plus three-quarters of the pancreatic head) was performed. In 2 patients, an extended pancreatic head resection with partial resection of the pancreatic body left of the upper mesenteric vein was performed.

Table 3 also summarizes the size of resected pancreatic tissue mass and the individual descriptive pathohistological key features of all patients. It seems to be noteworthy that in 4 patients single or multiple non-encapsulated microadenoma-like nodules within a range

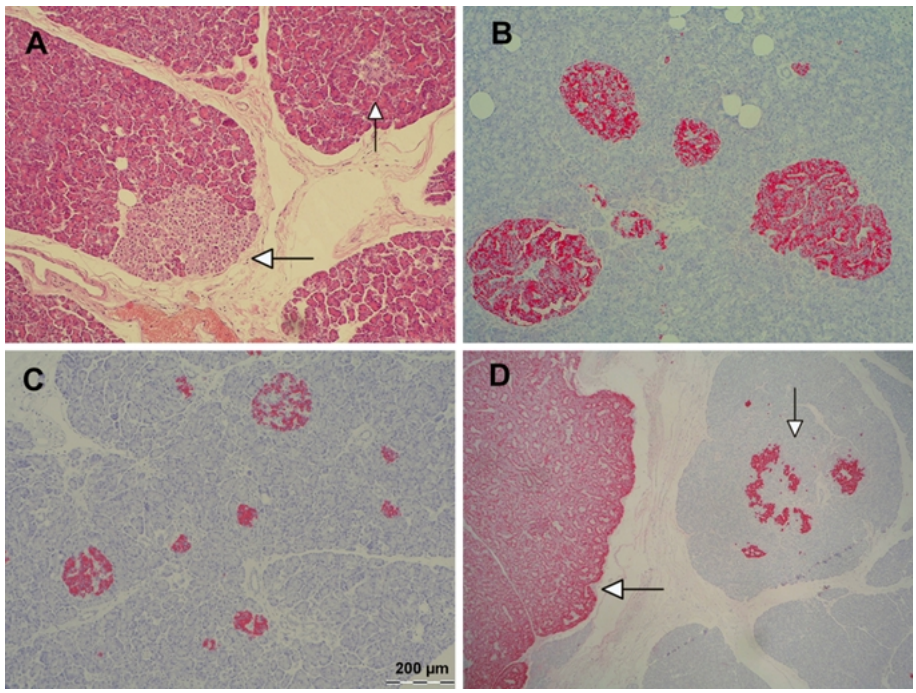

Figure 1. Histology (**A.** HE stain) and anti-insulin immunohistochemistry stains (**B**–**D.**) from 4 different patients with islet hyperplasia/islet hypertrophy. **A.** Patient #5, HE stain (magnification, ×100), *arrows* indicate a normal and an enlarged hypertrophic islet. **B.** Patient #9, cluster of polymorph hypertrophic and hyperplastic islets (magnification, ×100). **C.** Patient #7, two enlarged hyperplastic islets measuring ~200 μm as indicated by the scale bar (magnification, ×100). **D.** Patient #10, *arrows* show the border of one of several non-encapsulated microadenomas measuring 3 mm in diameter as well as a cluster of irregularly shaped islets (magnification, ×45).

of 1–6 mm were detected microscopically. Figure 1 shows typical islet hyperplasia and islet hypertrophy (Fig. 1A–C) as well as a section of a microadenoma (Fig. 1D) from 4 different patients.

Postoperative Functional Results

Postoperatively, 2 patients developed mild diabetes mellitus to be controlled by preprandial short acting insulin (#5, #11), and 1 patient (#7) only recently complained of typically recurrent hypoglycemic symptoms. One patient with a three-quarter resection (patient #9) has gone back to competitive long distance running.

DISCUSSION

The existence of hypoglycemia due to nesidioblastosis or islet hyperplasia and hypertrophy in adults has been a controversial issue among clinicians and pathologists for decades. The clinical entity of NIPHS as a novel syndrome of hypoglycemia from diffuse beta-cell hyperfunction was first described by Service *et al.*[11–13] An initial 10 patients presented with postprandial neuroglycopenia, but a negative standard supervised fasting test. In addition, pathohistological evidence of islet hypertrophy and islet hyperplasia as well as endocrine cell budding off the ductular epithelium similar to nesidioblastosis in infancy and the genetically linked PHHI (persistent hyperinsulinemic hypoglycemia of infancy) were seen. The incidence of insular hyperplasia and/or nesidioblastosis has previously been reported in large published series within the range of 1.5%–5%.[8,17]

Hypoglycemia due to non-insulinoma beta-cell hyperfunction in adults is a rare but clinically important disease.[18–25] Attempts should be made by any means to preoperatively differentiate it from solitary benign insulinomas of the pancreas in order to prevent failure of the surgical intervention.[4,26] In six studies with a combined number of 635 patients published during the last 10 years, we estimated an incidence of non-insulinoma hypoglycemia due to histological islet abnormalities of 5.3%[9,11,13,18,20,26] probably including a substantial number of patients with NIPHS. In tertiary referral centers this rate may rise to more than 20% (17 out of 77 patients).[27] According to our own experience, we estimated a frequency of 3 out of 93 patients (3.2%) between 1975 and 2000, and rising to 8 out of 20 patients (40%) since 2001 (total incidence 11 out of 113 patients; 9.7%).

Taking into account the increasing number of patients with obvious NIPHS that have been reported in the literature, [11–13,18] we compared the 11 patients reported here with 70 of our patients successfully treated for a benign single insulinoma and an additional 70 patients in whom a hypoglycemic disorder was excluded. We questioned whether specific clinical and biochemical data might point toward a preoperative diagnosis of NIPHS rather than a pathohistological diagnosis. From the literature,[4,8,9,11,12,17–26,28–38] we estimated a mean age of 44 years in 64 patients with NIPHS compared with 41 years in our series of 11 patients and 49 years in our 70 patients with insulinoma. NIPHS has been reported to occur throughout the lifespan from 11 to 84 years and there was a female preponderance (39 women, 25 men).

The diagnosis of NIPHS has to be considered in all patients with proven endogenous hyperinsulinemic hypoglycemia with negative localization studies using ultrasonography, CAT scans or NMR. This, however, is not specific to NIPHS since approximately 30% of patients with a single insulinoma also fail to show a pancreatic tumor preoperatively.[10,37] Specific reference to the results of localization studies was available in 36 of the 64 patients from the literature with positive findings in the pancreas in 9 patients (25%), falsely interpreted preoperatively as a single insulinoma. This was evident in 6 of our 11 patients with NIPHS, too, rendering localization studies rather unspecific in any attempt to differentiate NIPHS from patients with a single insulinoma.[39] Thus, a functional differentiation between these two different hypoglycemic disorders seems to be warranted and has been effected by Service *et al.*[11] The authors characterized patients with NIPHS by postprandial neuroglycopenia and a negative 72-h fasting test. Furthermore, 6 patients had been treated for massive obesity by means of a gastrojejunal bypass operation prior to the development of islet hyperplasia.[13] Until now, the functional differentiation between NIPHS and patients with insulinoma has not been addressed in the literature. Only 2 of our 11 patients had negative 72-hour fast and postprandial hypoglycemia during the OGTT. Both patients were obese (Table 1). We describe for the first time rather low serum insulin levels close to the conventionally considered limit of complete and adequate suppression (3 mU/l) at the time of postprandial and/or fasting hypoglycemia in most patients with NIPHS compared with patients with an insulinoma (Table 2). Only 1 patient (#6) demonstrated a serum insulin level above 15 mU/l at the time of hypoglycemia during the standard fast, which was obvious in the majority of the 70 patients with a single insulinoma (n = 52; 71%). We are aware that over the years lower serum insulin levels are partially due to the changed insulin assay technology since the standard unspecific radioimmunoassay has been replaced almost worldwide by specific ELISAs that do not cross-react with proinsulin. Therefore, proinsulin levels were consequently estimated as of 2001 in all our new patients. The proinsulin concentration was elevated well above 10 pmol/l during postprandial hypoglycemia in all patients, but less frequently during fasting hypoglycemia. However, reported proinsulin levels in patients with insulinoma often exceed 100 pmol/l at the time of fasting hypoglycemia.[14]

Patients with NIPHS who presented with postprandial neuroglycopenia during the OGTT tended to counterregulate the low blood glucose levels appropriately in contrast to patients with insulinoma. This is untypical for patients with insulinoma, who frequently suffer from seizures due to severe hypoglycemia and more pronounced hyperinsulinemia.[1,4,38,40,41] Until now spontaneous recovery from low blood glucose levels has been described distinctively only in patients with familial hyperinsulinemic hypoglycemia caused by stimulating mutations of the glucokinase gene.[42] It was not found in other patients with familial hypoglycemic syndromes, such as in PHHI patients with sulfonylurea receptor-1 (*SUR-1*) and potassium inward rectifier 6.2 gene (*Kir6.2*) mutations or in MEN-1 patients with single or multiple insulin-secreting tumors.[19] We assume that more than a single distinct pathophysiological lesion and likely mutations of other genes involved in insulin secretion may characterize the rare entity of patients with NIPHS despite a similar functional dysregulation of pancreatic beta cells. Therefore, it is not surprising to find a broad spectrum of pathohistological and morphometric changes in beta cells and pancreatic islets of these patients.[27] These are focally and diffusely distributed multiple small adenomas, beta cell adenomatosis, islet cell hypertrophy and islet hyperplasia, as well as beta cell hypertrophy and hyperplasia.[18,27,30,31,34] Some studies use the definition of nesidioblastosis, primarily attributed to pancreata of infants with specific beta cell changes caused by distinct mutations.[7–9,20,22–24,32,34] These attempts to define islet pathology from potentially true patients with NIPHS morphologically or morphometrically[18] have to face the fact that similar differences in pancreatic islets and endocrine islet cells can also be found substantially in normal pancreata, as has been described by Goudswaard *et al.* in 1984.[28] This also includes the possible coincidence of single adenomas and signs of focal or diffuse islet cell changes as described by Rossi *et al.*[25] and Chen *et al.*[31]

Table 4.
Results of surgery in patients (n = 64) with non-insulinoma pancreatogenic hypoglycemia syndrome (NIPHS, islet hyperplasia, nesidioblastosis) according to the literature.[4,8,9,11,12,17–26,28–38]

Extent of pancreatic resection	Patients n (%)	Cure n (%)	Pers/rec hypo n (%)	DM n (%)	Reop. n (%)
Partial resection <60%	25 (39)	8 (32)	16 (64)	1 (4)	8 (32%)
Extended left/right resection 70%–75%	28 (44)	10 (36)	14 (50)	4 (14)	1 (4%)
Subtotal/total pancreatectomy >90%	11 (17)	2 (18)	–	9 (82)	–
Total	64 (100)	20 (31)	30 (47)	14 (22)	9 (14%)

Pers/rec hypo: persistent/recurrent hypoglycemia; DM: diabetes mellitus; Reop.: reoperation.

When NIPHS is suspected, preoperative localization or at least regionalization of the involved pancreas mass is needed to guide surgical resection procedures. The most useful preoperative investigation in this respect seems to be the selective arterial calcium stimulation with venous sampling of serum insulin from the right hepatic vein (SAVS). This test can detect a pathological increase in serum insulin after bolus calcium stimulation and may differentiate between involved regions of the head, body, and tail of the pancreas.[3,21,35,43,44] SAVS additionally proves islet cell dysregulation, since the test is negative in a normal pancreas.[45] The only misinterpretation of a pathological SAVS test has been reported in a female patient with chronic metformin ingestion due to felonious intoxication by her husband.[46]

Despite clinical and biochemical evidence for underlying NIPHS and regionalization of pathological insulin secretion by means of a SAVS test, it is still rather unclear which amount of pancreatic resection may accomplish the best postoperative outcome. We retrospectively analyzed 64 published cases from the literature of assumed non-insulinoma hypoglycemia excluding our 11 patients. These 64 patients[4,8,9,11,12,17–26,28–38] have had limited resection below 60% in 25 cases (39%), an extended left-sided resection or right-sided Whipple's procedure with resection of approximately 70–75% of the pancreatic tissue in 28 patients (44%), and a subtotal to total (>90%) pancreatic resection in 11 patients (17%; Table 4). Cure rate, persistence and recurrence of hypoglycemia as well as postoperative incidence of diabetes mellitus are shown for different resection procedures with a total of 20 patients (31%) being cured, 30 patients (47%) with persistent or recurrent hypoglycemia, and 14 patients (22%) with postoperative insulin-dependent diabetes mellitus. Eight out of 25 patients (32%) with limited pancreatic resection had to be reoperated because of severe postoperative hypoglycemia and 2 of them had to be operated more than once. In our 11 patients a limited resection was performed in 6 patients (55%) whereas an extended 70%–75% resection had been performed in 5 (45%). One patient recently complained of mild recurrence of symptoms, typical of hypoglycemia, after many months of being well. Two patients developed a mild form of diabetes mellitus postoperatively whereas 8 patients (73%) are presently euglycemic and cured of their disease. This cure rate is definitely better than figures reported in the literature with 20 out of 64 patients (31%). The reason for this difference is unclear, but may partially be explained by differences in the postoperative follow-up, which is as yet rather short in our series. The latter assumption is questionable, however, since most patients with failed surgical intervention presented with persistent or early recurrent hypoglycemia within the first year of surgery.

In summary, we describe our experience in 11 patients with non-insulinoma pancreatogenic hypoglycemia syndrome and address the possibility of preoperative differentiation between patients with NIPHS and patients with single insulinomas by means of a combined oral glucose tolerance test followed by a prolonged fast for up to 72 hours. The lower serum insulin levels in patients with NIPHS compared with patients with single insulinomas were highly significant. This result with the additional regionalization of pancreatic tissue involved by means of the selective arterial calcium stimulation enabled us to more precisely plan resection procedures preoperatively with better results than a 30% probability of postoperative cure. The data also demonstrate the necessity of focusing on endocrine function in the future rather than mere morphological aspects when patients with NIPHS are investigated.

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