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Research Article

Follow-Up in Adult Patients with Pancreatogenic Hypoglycemia Caused by Sporadic Micro- or Macro- Insulinomatosis - 16 Years of Experience in One Center

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Abstract

Purpose: Sporadic multiple insulinomas and regional nesidioblastosis (together defined as "Insulinomatosis") are rare causes of hypoglycemia. Treatment options and postoperative outcome are discussed to define future strategies.

Methods: We retrospectively analysed patients with Neuroendocrine Tumours (NEN) and hypoglycemia, treated between 2001 and 2017. Data related to diagnosis and to therapy were evaluated. Postoperative outcome (diabetes mellitus, relapse of hypoglycemia) was measured and Quality of Life (QoL) was assessed by standardized questionnaires and telephone interview.

Results: Ninety-eight patients demonstrated with NEN causing hypoglycemia. 78 (79.6%) showed an insulinoma and 20 (20.4%) suffered from insulinomatosis, with no prior bariatric surgery. The 15 female and 5 male patients showed a median age of 45.5 years (range 24-70). 15 of 20 patients (75%) with insulinomatosis were operated on (left/ extended left resection n=12, modified Whipple's procedure n=2, uncinate plus left resection n=1) and five (26%) had been treated conservatively, only. Median follow up was 53 (range 6-121) months. 6 of 15 patients (40%) suffered from recurrent disease, diagnosed 11.5 months (range 5-36) after surgery. 4 patients (26.7%) were re-operated, one (6.7%) had a second recurrence. 3 of 15 patients developed Diabetes mellitus (20%). Overall QoL improved in 10 (66.7%) and worsened in 4 patients (26.7%) (unknown in one patient, who died from myocardial infarction).

Conclusions: Only few patients with insulinomatosis can be treated conservatively. The majority of patients operated on by 80% pancreatic resection show relief from symptoms and improved quality of life, but in some hypoglycemic recurrence may occur.

Keywords: Insulinomatosis; NIPHS; Pancreatectomy

Introduction

Modern laboratory investigations as well as precise localization techniques have elucidated a rare and specific form of sporadic pancreatogenic hypoglycemia in adults, pathologically defined as "Insulinomatosis" by M. Anlauf et al., in 2009 [1]. Thus, it has been known that hyperinsulinemic hypoglycaemia can be caused by single sporadic benign and malignant insulinomas or by single and multiple insulin-producing tumors in patients with familial multiple endocrine neoplasia type I (MEN-I syndrome) (see Table 1). Additionally, to these Service et al. in 1999 described a regional or diffuse insulinomatosis in adults, years after surgical treatment of malignant obesitas by gastric bypass operation (NIPHS) [2]. This form of nesidioblastosis is different to this in newborns and in young children as it lacks mutations in potassium channel genes, which have been described in nesidioblastosis of infants (SUR 1 and Kir 6.2) [1-6]. Adults with insulinomatosis, however,

described by Anlauf et al. [1] and Starke et al. [7], are easily separated from patients with NIPHS, as they never had suffered from malignant obesitas before nor had they undergone a gastric bypass operation. Additionally, we noticed that the clinical pictures and most Oral Glucose Tolerance Tests (OGTT) are rather specific for insulinomatosis patients, different to these of patients with single insulinomas, as it has been described earlier by us [7,8].

Pancreatogen	- Diabetes mellitus
	- Insulinoma
	- Multiple Endocrine Neoplasia type I (MEN-I)
	- Insulinomatosis
Other	- dumping after gastric surgery
	- bariatric surgery
	- medications (insulin, sulfonylureas, etc.)
	- alcohol
	- adrenal insufficiency, malabsorption, coeliac disease
	- serious internal diseases (e.g., cardiac, renal, hepatic, septic)
	- exercise hypoglycemia
MEN: Multiple Endocrine Neoplasia type	

Table 1: Differential Diagnosis of Hypoglycemia.

Long term outcome in these patients still is questionable, however, as former studies on patients with insulinomatosis, starting with that of Harness et al. in 1981, mainly described patients with persistent and recurrent hypoglycemia because of suspected insulinoma and unknown insulinomatosis [9]. None of these patients had been diagnosed to suffer from insulinomatosis, before the primary ineffective pancreatic surgery. Since 2001 we were aware of this problem and detected possible insulinomatosis preoperatively (negative tumor localization, rather specific OGTT). We now questioned, whether short and long-term results in patients with preoperatively diagnosed insulinomatosis would differ from this, of patients being treated before.

Material and Methods

Preoperative Suspicion of Insulinomatosis

For the diagnosis of insulinomatosis various prerequisites had to be fulfilled. First diagnosis of pancreatogenic hypoglycemia had to be proven by venous blood glucose levels < 40 mg/dl and insulin/proinsulin levels > 3mU/l or > 5 pmol/l and a measurable c-peptide at times of symptoms that resolved with glucose intake (Whipple's triad) (Table 2). Additionally, an oral glucose tolerance test was demanded in questionable cases, as they are rather specific for many patients with insulinomatosis.

Blood Glucose (BG) (mg/dl)
Insulin at BG minimum and maximum (mU/l)
C-peptide (ng/ml)
Proinsulin (pmol/l)
HbA1c (%)
Others (creatinine, liver parameters, c-reative protein, uric acid, triglycerids, cortisol, GH, IGF1 etc)
Urine (for ketone bodies and organic acids)
Detailed: Insulin secretion profile 0-360 min or >

Table 2: Laboratory test for hypoglycemia [3,7].

OGTT-Fasting Test and Imaging

Glucose co-underregulation in OGTT may differentiate between patients with insulinomatosis and those with single isolated insulinoma, since serum hormone levels are rather low in insulinomatosis and patients subsequently may even fast for up to 72 hours without developing hypoglycemia, (Figure 1) [7].

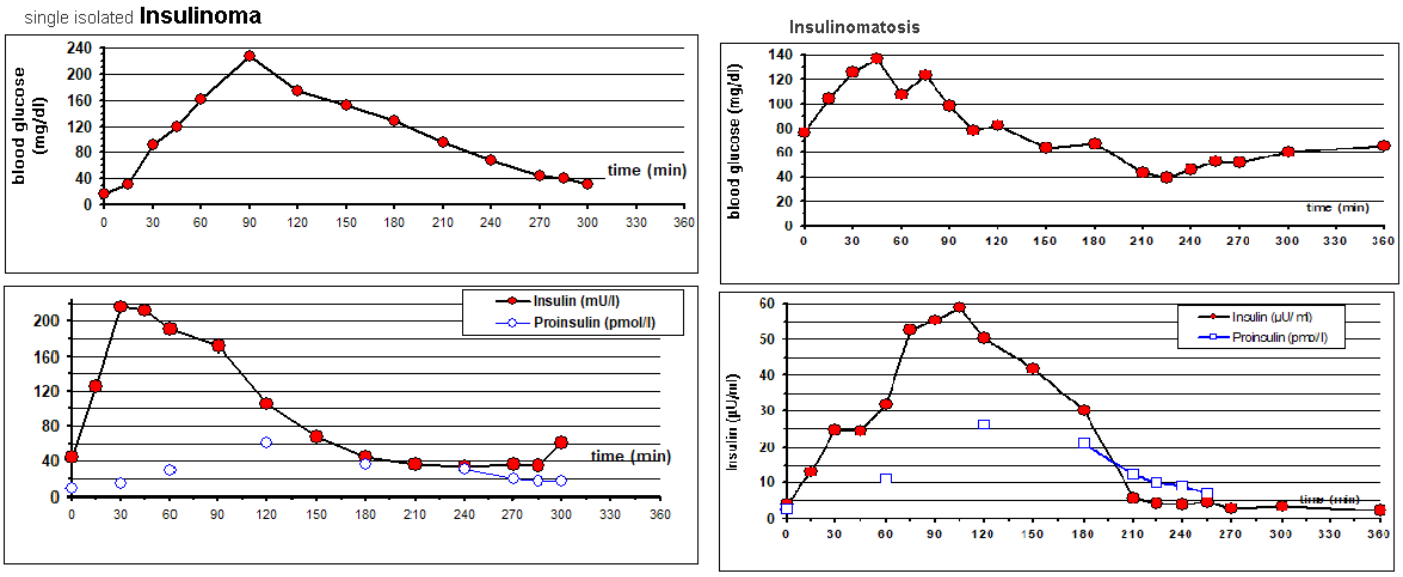

Figure 1: Typical pattern of secretion in the OGTT for insulinomatosis and single isolated insulinoma.

All OGTT were performed by one of the authors (A. Starke), personally. Starting the OGTT blood was drawn for serum glucose, insulin, proinsulin, c-peptide and patients was given 75g glucose orally (drink). Then serum glucose and insulin plus proinsulin levels were measured every 15 minutes for 4 hours, followed by 30-minute intervals until patients became symptomatic or blood glucose levels reached 50 mg/dl or less. Further progress in OGTT was dependent on clinical symptoms and serum glucose levels. The fasting test was considered positive when blood glucose levels dropped under 40 mg/dl while pathological insulin and c-peptide levels were documented (Figure 1) [7].

After the typical clinical history and a positive OGTT fasting test further workup included localization of possible pancreatic tumors by use of endosonography, CT and/or MRI. In case of positive OGTT but negative localization studies calcium stimulation test (SACI) and/or 18-F-DOPA-PET-CT was performed, as described by Starke (Table 3) [7,8].

	Insulinoma	**Insulinomatosis**
Whipple's triad	+	+
OGTT	6h-OGTT to hypoglycemia	postprandial +, selflimiting hypoglycemia
Fasting test	Positive	Negative
Preoperative localisation	Positive	Negative
SACI	Positive	Positive
Operation	enucleation / resection	distal pancreatectomy (80%)
Histopathology	single neuroendocrine tumour	non-single-insulinoma: multiple tumours, ß-cell hypertrophia and hyperplasia
OGTT: Oral-Glucose-Tolerance-Test, SACI: Selective Arterial Calcium stimulation with venous sampling test		

Table 3: Diagnostic and Differential Diagnosis.

Surgical Treatment of Insulinomatosis

In contrast to single insulinoma patients, where surgery aims for the least aggressive procedure, patients with insulinomatosis will always undergo a rather wide pancreatic resection between 60-90% to prevent persistent or recurrent hypoglycemia [7,10,11].

Regionalisation of insulinomatosis to the pancreatic head or pancreatic tail by SACI-test or 18-F-DOPA-PET-CT was followed by distinct surgical procedures of subtotal left sided (distal) pancreatectomy or an extended pylorus preserving Pancreatoduodenectomy (PPPD). To confirm negative preoperative localisation studies in insulinomatosis patients prior to resection an extended Kocher`s manoeuvre was performed intraoperatively, followed by bidigital palpation and Intraoperative Ultrasonography (IOUS) of the whole organ. This was always performed to rule out single or multiple pancreatic tumours. The resection margin of left sided subtotal pancreatectomy was closed with monofil 4x0 PDS suture and separate closure of the pancreatic duct. In some patients, fibrin glue or a fibrinogen fleece was placed on the area of resection, additionally. As an alternative, either the posterior gastric wall, or parts of the omentum majus were fixed to the pancreatic tissue at the resection margin. All patients received a drain, which remained until termination of high amylase secretion. 30 days and total hospital mortality was measured, as well as typical postoperative complications such as pancreatic fistula disease A-C, postoperative bleeding, other indication for re-intervention, and secondary wound healing.

Follow-up

In between a mean follow-up of 10.9 years (2-16 years) patients were questioned concerning clinical symptoms of recurrence (which period (months, years) after operation, with which symptoms (after meal or spontaneous), development of diabetes, intestinal symptoms like diarrhoea, use of medication for hormonal suppression (such as somatostatin analoga), need for specific diets, and final outcome. Additionally, questions were addressed by phone investigating the subjective quality of life estimation of each patient before and after their pancreatic surgery (Table 4).

1)	Did hypoglycaemia relapse after operation?
-	If yes, when for the first time after operation?
-	Please describe your symptoms.
-	When do the symptoms appear? After a meal? After which meal? Regardless of a meal?
-	Do you still measure your blood glucose level (BG)? How often?
-	Was the blood glucose under 40, 50, 60 mg / dl? Have you or your doctor documented the BG?
-	How was hypoglycemia treated?
2)	Has Diabetes mellitus been diagnosed?
-	If yes, when?
-	Has your doctor documented the HBA1c?
-	Has an insulin or non-insulin medication been introduced (dosage)?
3)	Have your received somatostatin analoga (dosage)?
4)	Do you suffer from indigestion/ diarrhoe/ flatulence/ abdominal pain?
-	How often (daily/ weekly)?
-	Do you take pancreas enzymes (dosage)?
5)	Quality of life: has your quality of life changed due to the operation?
-	Better (++), good (+) or worse (-)?

Table 4: Questionnaires.

Results

From 2001 to 2017, 262 patients with Neuroendocrine Neoplasia (NEN) were diagnosed and treated in our department. 98 patients (37.4%) with pancreatogenic hypoglycemia were diagnosed, of whom 20 patients (20.4%) demonstrated with insulinomatosis, and 78 patients (79.6%) with a single insulinoma. Of the 20 patients with insulinomatosis 15 (75%) were female and 5 (25%) were male. The median age at time at operation was 46 years (24-70 years), table 5.

Patient	Year	Sex/Age	1.operation	Complication	Recurrence time (months)	2.op, date (months),3. re-op	Final outcome	QOL
S.S.	2001	F/ 34	Left (80%)	-	12	no re-op	Hypoglycemia	-
B.C.	2002	F/ 67	Traverso	-	36	120, subtotal	Euglycemia	+
B.S.	2002	F/ 43	Left (80%)	p. fistula	-	-	Diab. Mell.	Unknown (Dead)
R.A.	2003	F/ 45	Left (80%)	pneumonia	-	-	Euglycemia	+
B.M.	2004	F/ 41	Left (80%)	-	-	-	Euglycemia	++
F.R.	2004	F/ 43	Left (80%)	p. fistula	6	no re-op	Hypoglycemia	-
B.F.	2004	F/ 46	Left (80%)	p. fistula	-	-	Euglycemia	++
R.S.	2005	F/ 30	Traverso	pneumonia	11	11, left	Diab. Mell.	-
S.K.	2005	F/ 70	Left (80%)	-	-	-	Euglycemia	+

J.I.	2006	F/ 41	Left (80%)	-	-	-	Euglycemia	+
K.K.	2007	M/ 53	SPTX (90%)	p. fistula	-	-	Diab. Mell.	++
B.U.	2009	F/ 53	Left (60%)	splenic infarct	5	5, subtotal	Hypoglycemia re-op??	-
B.AK.	2010	F/ 24	Left (70%)	-	-	-	Euglycemia	+
P.T.	2012	F/ 54	Left (70%)	pancreatitis	24	40, subtotal	Euglycemia	+
R.M.	2017	M/ 34	Left (80%)	-	-	-	Euglycemia	+
C.W.	2006	M/ 57	N					
F.K.I	2008	F/ 52	N					
H.S.	2010	M/ 32	N					
S.U.	2015	F/ 48	N					
W.J.	2015	M/ 31	N					
					Recurrence: 6/15 (40%)		Hypoglyc: 3/15 (20%)	Better: 3/15 (20%)
							Diab.mell.: 3/15 (20%)	Good: 7/15 (46.7%)
							Euglycemia: 9/15 (60%)	Worse: 4/15 (26.7%)
							Recurrence: 1/15 (6.7%)	Unknown: 1/15 (6.7%)

F: female, M: male, p. fistula: pancreatic fistula, Left: 80% distal pancreatectomy, SPTX: subtotal pancreatectomy, Diab. Mell.: diabetes mellitus, re-OP: re-operation, mon: months, + : good, ++ : better, - : worse.

Table 5: 20 patients with insulinomatosis were treated from 2001 to 2017 with 15 undergoing surgery. Demographic data, operative procedure, complications and outcome are listed in the table.

The diagnostic criteria suggesting an insulinomatosis or non-single insulinoma pancreatogenic hypoglycemia, preoperatively, were: 1. transient symptomatic postprandial neuroglycopenic hypoglycemia with a mean serum glucose level of 38 (23-44) mg/dl under provoked circumstances during OGTT was proven in 15/20 (75%). Lowest serum glucose during OGTT-fasting test was seen at 230 (150-360) min after glucose ingestion with inappropriately elevated mean levels for insulin of 6.1 (3.0-19.2 at normal glucose levels) mU/l, for c-peptide of 2.7 (1.1.-5.6 at n.g.l.) ng/ml, and for proinsulin of 24 (6-44 at n.g.l.) pmol/l; 2. insulinoma was biochemically excluded by a normal fasting test (absence of hypoglycemia < 40 mg/dl or low insulin/proinsulin < 3mU/l, < 5 pmol/l); 3. negative conventional imaging; 4. positive SACI-test gradient of 3.0 (1.4-4.5) measured in 16/20 patients; 5. positive PET/CT with ^{18}F-DOPA, performed in 4/20 patients, table 6.

Patient	Year	OGTT	EUS	CT	MRI	Octreotid-Scan	SACI	18F-DOPA-PET	IOUS	Intraop Palpation
S.S.	2001	+	-	-	n.d.	n.d.	+	n.d.	-	-
B.C.	2002	+	+	-	n.d.	n.d.	+	n.d.	-	-
B.S.	2002	+	+	-	n.d.	n.d.	+	n.d.	-	-
R.A.	2003	+	-	-	n.d.	n.d.	n.d.	n.d.	-	-
B.M.	2004	+	-	-	n.d.	n.d.	n.d.	n.d.	-	-
F.R.	2004	+	-	-	n.d.	n.d.	+	n.d.	-	-
B.F.	2004	+	n.d.	n.d.	n.d.	n.d.	+	n.d.	-	-
R.S.	2005	+	n.d.	n.d.	n.d.	-	+	n.d.	-	-
S.K.	2005	+	+[f]	-	n.d.	n.d.	n.d.	n.d.	-	-
J.I.	2006	+	-	-	n.d.	n.d.	+	n.d.	-	-
K.K.	2007	+	-	-	n.d.	n.d.	+	n.d.	-	-
B.U.	2009	+	+[f]	-	-	-	n.d.	+	-	-
B.AK.	2010	+	-	n.d.	-	-	+	+	-	-
P.T.	2012	+	-	-	+[f]	n.d.	+	n.d.	-	-
R.M.	2017	+	-	n.d.	-	n.d.	+	n.d.	-	-
C.W.	2006	+	-	-	-	n.d.	+	n.d.		
F.K.I	2008	+	-	-	-	n.d.	+	+		
H.S.	2010	+	-	-	-	n.d.	+	+		

S.U.	2015	+	-	-	-	n.d.	+	n.d.		
W.J.	2015	+	-	-	-	n.d.	+	n.d.		

OGTT: Oral Glucose Tolerance Tests, US: Ultrasonography, EUS: Endosonography, CT: Computer Tomography, MRI: Magnetic Resonance Imaging, SACI: calcium stimulation test, 18F-DOPA-PET: 18F]-L-dihydroxyphenylalanine Positronen-Emissions-Tomography, IOUS: intraoperative ultrasonography, Intraop: intraoperative, +: positive, -: negative, +f: false positive, -f: false negative, n.d.: not done, ?: questionable.

Table 6: Preoperative Diagnostic Procedure (first operation).

In 5 of 20 (25%) patients with mild symptoms of insulinomatosis modification in their diet sufficiently abolished their symptoms and there was no need for any medical therapy like sandostatin or diazoxide nor for any surgical intervention. The majority of our patients (n=15/20; 75%) were operated on, (Table 5). Since all our patients with insulinomatosis in 2001-2017 were preoperatively suspected to have insulinomatosis or non-single insulinoma hypoglycemia they were all operated on by a wide pancreatic resection, (Table 5).

Of these, 3 (20%) underwent a 70% distal pancreatectomy, 9 (60%) an 80% distal pancreatectomy and one patient (6.7%) a subtotal pancreatectomy (90%), respectively. In two patients (13.3%) a head and neck resection were necessary because of pathological islets in both areas, ending up in a Whipple's procedure (Traverso) for both. The average hospital stay was 18 days (10-34 days).

Histology

The histopathological examinations showed typical pattern of insulinomatosis with hypertrophic and hyperplastic beta cells and multiple small tumours, but without a solitary insulinoma in all patients, figure 2. In one patient, 10 years after last operation an additional insulinoma of 10 mm was detected at re-operation.

Postoperative Follow-Up

We questioned, whether the increased preoperative information of a regionally defined insulinomatosis and consequent specific surgical intervention may have altered the formerly high rate of persistent and recurrent hypoglycemia and whether this may have had an impact on their quality of life, as well, (Table 4).

There was no death during the hospital stay and in between 90 days postoperatively. 7 of 15 patients (46.7%) had no postoperative complications, table 5. 4 patients (26.7%) developed pancreatic fistulas (type A-B) postoperatively, which were successfully resolved without further operation by drainage and antibiotic therapy. There was no grade C fistula. Pancreatitis developed in one patient and 3 patients (20%) suffered from non-pancreatic complications, such as pneumonia (n=2) and splenic infarction (n=1), respectively.

Long-Term Follow-Up

3 patients (20%) (Traverso n=1, 80%-distal n=1 and subtotal pancreatectomy n=1) developed Diabetes mellitus within 12 months after surgery. Their HbA1c was 8.9 % (5,7-8,9%) under treatment with insulin and metformin.

In 6 of 15 patients (40%) hypoglycemia recurred with a mean interval of 11.5 months (5-36 months) after surgery. Hypoglycemia appeared spontaneously and independently from meals with glucose intake causing rapid improvement in all cases. 4 of 6 patients with recurrent hypoglycemia had to undergo second surgery 5-120 months after primary resection (mean 25.5 months). Subtotal pancreatectomy was performed in 3 patients and left resection in one. Two had been cured with euglycemia, the other patient had mild postoperative Diabetes mellitus. In one patient hypoglycemia developed again, 5 months after reoperation. Neuroglycopenic symptoms with blood sugar levels in the lower normal range (between 50-60 mg/dl) occurred only after physical and/or emotional stress and improved rapidly after glucose intake. 10 of 15 patients (66.7%) reported a significantly improvement in symptoms and quality of life and were fully reintegrated in their professional and social life again. Only 4 patients (26.7%) presented with no subjective benefits to surgery, and even complained of a general deterioration of their quality of life, postoperatively (Table 5).

Problematic Cases with Hypoglycemic Recurrence

Case 1

A 34-year-old female patient underwent an 80% left resection of the pancreas. 12 months later the patient developed hypoglycemia again, and a re-operation was performed. Nevertheless, she reported of persisting hypoglycemic episodes (BG < 40 mg/dl). After supply of glucose no hypoglycemia occurred. The patient has been pensioned early. She denied any further operative treatment.

Case 2

A 43-year-old female patient, who had been operated was diagnosed with recurrent disease 6 months after the initial operation. After re-operation her QOL was worsened due to persisting hypoglycemia (BG 24-49 mg/dl). The hypoglycemia improved after glucose feeding.

Case 3

A 30-year-old female patient underwent pancreatic head and neck resection (Whipple`s procedure after Traverso). She developed hypoglycemic recurrence after 11 months and was reoperated by a left-pancreatic resection. Following this she was left with a short pancreatic middle console, developing diabetes

mellitus (HbA1c 5,7-8,9%).

Case 4

In a 53-year-old female a 60%-left-resection of the pancreas was performed. 5 months later she developed hypoglycemia again. As hypoglycemia persists (BG 40-50 mg/dl) after a subtotal resection (80%) a further pancreatic resection is planned.

Case 5

One patient with postoperative Diabetes mellitus died after a myocardial infarction, two years later after the pancreatic operation.

Case 6

24 months after 70%-left-resection the 54-year-old woman developed hypoglycemia again. After subtotal resection she had no problems any more.

Discussion

The present study retrospectively analysed short and long-term outcome as well as quality of life in 20 patients with sporadic insulinomatosis, being treated during the last 16 years. To our knowledge it is the first study of more than one or two patients, with this disease who had been diagnosed preoperatively and thus had been treated in knowledge of this distinct form of pancreatogenic hypoglycaemia caused by insulin and proinsulin hypersecretion of regionally assembled pathologic islets. 15 of 20 patients had been operated on by extended pancreatic resection and three were treated conservatively. Long-term outcome and quality of life has been assessed as well.

Until now no comparable long-term result of patients with known sporadic "Insulinomatosis" and no prior gastric bypass surgery for obesity has been reported, so far. To our knowledge the only experience with insulinomatosis patients derives from unsuccessful operations of assumed single insulinoma patients with postoperative persistent and recurrent hypoglycemia [2,12-14]. Similar experience in patients with regionally gathered forms of pathological islets has been reported from patients with hypoglycemia after gastric bypass operation for malignant adipositas, suffering from diffuse islet hyperplasia. This disease was named Non-Insulinoma Hypoglycemia Syndrome (NIPHS) by Service et al [2,12,13] and is distinct to "Insulinomatosis", since none of our 20 insulinomatosis patients ever suffered from malignant adipositas before nor underwent any of these patients a gastric bypass operations. Both groups of patients suffer from a sporadic disease of regional assembled pathologic islets, hypersecreting insulin and proinsulin, clinically and in response to a calcium stimulation test (SACI).

In 2010 Vanderveen et al reported long-term results in 48 operated patients with NIPHS [14]. They demonstrated a recurrence rate of clinically important pancreatogenic hypoglycaemia in 87% of these patients after partial pancreatectomy. This was observed after a median interval of only 16 months after surgery. Despite these disappointing number of high recurrence, the majority of their patients reported an improvement of their QOL. Only 25% denied an advantage from the operation. For these patients, nowadays, surgical revision of gastric bypass surgery eliminates hypoglycemia [17].

In comparison to their findings, recurrence rate in our patients was only 40%. Hypoglycemic recurrence, if occurring, however, had been diagnosed rather early with a mean interval of 11.5 months (5-26 months) postoperatively. Final persistent disease after re-resection was 6.7%.

Altogether long term postoperative follow-up showed more patients developing hypoglycemia after periods of normoglycemia, as it has been described by us and others before [7,10,14]. In 2006 Starke et al showed that only one of 11 patients had experienced symptomatic relapse with a primary cure rate of 73% [7]. But the follow-up was short, and our long-term experience now demonstrates that 40% of our patients developed recurrent hypoglycemia. Despite the fact that we suggested (diagnosed) insulinomatosis preoperatively and performed extended pancreatic resections (aiming for approximately 80% pancreas resection) recurrence could not be eliminated, totally.

Published studies on this topic are of no help, whatsoever, since diagnosis of disease was performed postoperatively in most studies and there is no generally accepted operative strategy visuable. Neither we know, however, why some of our patients suffered from hypoglycemic recurrence, whereas others did not. There was no difference in age, sex, insulin levels at nadir, (Table 7).

Patient	Sex	Age	at (min)	BZ	Insulin levels at nadir	1.operation	Recurrence time (months)
With:							
S.S.	F	34	360	66	2.3	Left (80%)	12
B.C.	F	67	360	23	2.9	Traverso	36
F.R.	F	43	360	54	4.4	Left (80%)	6
R.S.	F	30	240	67	7.1	Traverso	11
B.U.	F	53	300	41	5.3	Left (60%)	5
P.T.	F	54	230	33	6.6	Left (70%)	24
Without:							
R.A.	F	45	240	39	2.8	Left (80%)	
B.M.	F	41	360	38	1.6	Left (80%)	
B.F.	F	46	300	33	3.8	Left (80%)	
S.K.	F	70	?	?	?	Left (80%)	
J.I.	F	41	360	68	4.6	Left (80%)	
K.K.	M	53	360	62	11	SPTX(90%)	
B.AK.	F	24	360	65	2.2	Left (70%)	
B.S.	F	43	240	37	2.6	Left (80%)	
R.M.	M	34	240	42	3	Left (80%)	
?: questionable.							

Table 7: Comparison of patients with/ without hypoglycemic recurrence.

We thus suspect that patients with insulinomatosis present an inhomogenic group of patients with a variety of pathologic and genetic abnormalities, leading to similar clinical pictures of spontaneous and postprandial pancreatogenic hypoglycemia. Therefore, surgical treatment with rather extensive pancreatic resection may be curative in some but not all of these patients.

Former discussion on the definition of patients with insulinomatosis (formerly often described as "Nesidioblastosis of the adult") focused on histological findings and images. Anlauf et al. [1] demonstrated multiple small insulinomas with islet hypertrophy and hyperplasia that almost exclusively expressed insulin and showed increased number of beta cells, which had been twice as large as the normal cells [1,4], (Figure 2). Even co-existence of an insulinoma and specific islet and beta cell hyperplasia has been described first by Kaczirek et al. [15] and afterwards also by Anlauf et al [1]. This we experienced in one of our 15 operated patients, as well. A- 67-year old women was operated on with histologically proven insulinomatosis and developed hypoglycemia recurrence, 3 years after primary surgery. A second operation was required, and histologic examination now demonstrated an islet cell hyperplasia with exclusive insulin secretion as well as an insulinoma of 10 mm in diameter.

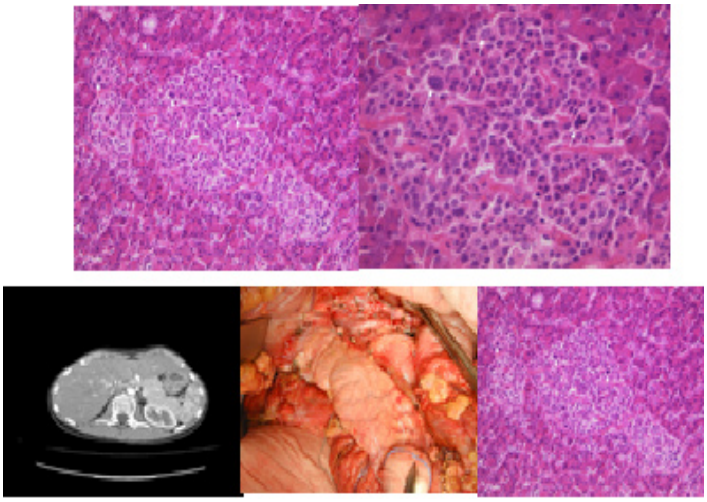

Figure 2: The histopathological examinations shows the insulinomatosis typical pattern of several hypertrophied islet cells with big nuclei (hyperplasia) and with multiple small micro - and macroadenomas, 50-500 µm of cells.

Therefore, a distinct clinical differentiation between small insulinoma and insulinomatosis as attempted by Service et al

or Starke et al, using the well-defined OGTT and following fast test, will help in most cases of single insulinomas but will not be successful in all [2,7,12]. Neither it can rule out the very rare cases of concomitant occurrence of insulinomatosis with small insulinomas.

Concerning the operative treatment Kaczirek et al described that the surgical procedure in insulinomatosis patients may differ completely from that of children with Nesidioblastosis and from that of patients with single insulinomas [15,16]. While in patients with insulinoma an enucleation may be sufficient, in patients with insulinomatosis a pancreas tail resection or even wider left side resection may be required. This rather equals the experience in children with regional insulinomatosis, where results vary significantly between different groups [15,16]. Despite the fact that such more extended resections maybe useful in insulinomatosis patients, the extent of pancreatic resection is not clearly defined. Restricted distal pancreatectomy is based on the results of the SACI-test, which serves as a gradient but mostly is followed by early hypoglycemia recurrence [7,10,11]. Good results are shown for 80% distal pancreatectomy [15]. Also, to our experience smaller resection (60%) may lead to relapses and/ or persistence of hypoglycemia are to be expected, while subtotal pancreatectomy (90%) leads to diabetes mellitus. Therefore, an approximately 80% pancreatic resection might be optimal in most patients with insulinomatosis. The majority of our operated patients, more than 66%, report a significant improvement in their Quality of Life (QOL) because of their relief from expectantly happening hypoglycemia episodes. Surgical treatment with euglycemia or even mild Diabetes mellitus allowed their return to normal life activities, such as school visits etc. and one patient even could restart her marathon activities as another started his long term desired pilgrim‘s trip. Vanderveen et al. described similar experience with 75% of their patients reporting an overall improvement in QOL, despite the fact that more than 80% of their patients developed recurrent hypoglycemic episodes, again [14]. Whether pancreatic surgery is treatment of choice in NIPHS patients seems more questionable than in patients suffering from insulinomatosis but for both the release from severe hypoglycemia lead to increased selfestheme and therefore improved QOL.

Conclusion

Our long-term results in 20 patients with insulinomatosis showed the positive effect of an 80% pancreatectomy, leading to relief of hypoglycaemia and to an improved quality of life in the majority of patients. Since postoperative recurrence as well as postoperative diabetes mellitus cannot be excluded, totally, long-term control of glucose metabolism is warranted. Further studies focussing on pathologic and genetic variations in insulinomatosis are needed to define patients that are not in need of operation at all and those, who are in danger of recurrence despite a large pancreatic gland resection.

Compliance with Ethical Standards

Conflicts of Interest: The authors have no direct or indirect commercial and financial incentive associated with publishing the article. There are no potential and real conflicts of interest.

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