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Neuroendocrine tumors – insulinoma in clinical practise

Guzy neuroendokrynne – *insulinoma* w praktyce klinicznej

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Summary

Introduction. Insulinoma belongs to the most functional pancreatic neuroendocrine neoplasms, with specific problems in their diagnosis, localization and treatment.

Aim. The aim of our study was to describe diagnostic problems, clinicians cope to correctly determine insulinoma.

Material and methods. We included 74 patients (52 females and 22 males) admitted to the Department of Endocrinology and Diabetology, Collegium Medicum in Bydgoszcz, University of Nicolaus Copernicus in Toruń between 2001 and 2010, because of clinical suspicion of insulinoma: weakness, sweating, blured vision, confusion and dizziness. They all were subjected to a 72-hour-fasting test, which is considered as the gold standard to recognize insulinoma.

Results. In our study the Whipple's triad (neurologic symptoms of hypoglycemia, blood glucose levels less than 40 mg/dl and immediate alleviation of symptoms after glucose ingestion) was present only in 10 of 74 patients (8 females and 2 males). We implemented ultrasonography, computed tomography, somatostatin receptor scintigraphy and endoscopic ultrasonography. Only in one of the patients with diagnosed insulinoma a single tumor (2 cm), situated on a border of head and corpus of pancreas, was localized with the use of the computed tomography. Also in two of the patients with the use of the endoscopic ultrasonography an insulinoma was recognized.

Conclusions. Treatment strategy of insulinoma is surgical removal of the tumor. A simple enucleation of the tumor is successful in over 90% of cases. The diagnosis of insulinoma is very difficult, despite available investigative methods.

Key words: insulinoma, 72-hour-fasting test, Whipple's triad, somatostatin receptor scintigraphy

Streszczenie

Wstęp. Insulinoma należy do najczęstszych nowotworów neuroendokrynnych trzustki z określonymi problemami w diagnostyce, lokalizacji i leczeni.

Cel pracy. Celem naszego badania było przedstawienie problemów diagnostycznych i klinicznych w rozpoznawaniu *insulinoma.*

Materiał i metody. Do badania włączyliśmy 74 pacjentów (52 kobiety i 22 mężczyzn) hospitalizowanych w Klinice Endokrynologii i Diabetologii Collegium Medicum w Bydgoszczy, Uniwersytetu Mikołaja Kopernika w Toruniu w latach 2001-2010 z powodu klinicznego podejrzenia *insulinoma*: osłabienie, potliwość, pogorszenie ostrości wzroku, splątanie i zawroty głowy. U wszystkich pacjentów wykonano 72-godzinny test głodowy, który jest uznany za złoty standard w rozpoznawaniu *insulinoma*.

Wyniki. W naszym badaniu triada Whipple'a (neuroglikopenia, obniżony poziom glukozy we krwi < 40 mg/dl, natychmiastowe ustąpienie objawów po przyjęciu glukozy) wystąpiła tylko u 10 z 74 pacjentów (8 kobiet i 2 mężczyzn). Wykonaliśmy badania obrazowe, takie jak: ultrasonografia, tomografia komputerowa, scyntygrafia receptorowa z użyciem analogu somatostatyny oraz ultrasonografia endoskopowa w całej grupie badawczej. *Insulinoma* uwidoczniono u jednego pacjenta za pomocą tomografii komputerowej (guz 2 cm usytuowany na granicy głowy i trzonu trzustki) oraz u kolejnych dwóch badanych osób przy użyciu ultrasonografii endoskopowej.

Wnioski. Docelowym leczeniem *insulinoma* jest chirurgiczne usunięcie guza, skuteczne w 90% przypadków. Jednak rozpoznanie *insulinoma* jest bardzo trudne, pomimo dostępności wielu metod.

Słowa kluczowe: *insulinoma*, 72-godzinny test głodowy, triada Whipple'a, scyntygrafia receptorowa z użyciem analogu somatostatyny

INTRODUCTION

Insulinoma belongs to the most functional pancreatic neuroendocrine neoplasms, with specific problems in their diagnosis, localization and treatment. Over 90% of the cases are caused by a single, usually benign, neuroendocrine tumor of the pancreas (1-6). The diagnosis of insulinoma should be considered if clinical symptoms of hypoglycemia occurred. The gold standard to recognize insulinoma is the 72-hour-fasting test, where the Whipple's triad is present (4, 7-9).

AIM

The aim of our study was to describe diagnostic problems, clinicians cope to correctly determine insulinoma.

MATERIAL AND METHODS

We included 74 patients (52 females and 22 males) admitted to the Department of Endocrinology and Diabetology, Collegium Medicum in Bydgoszcz, University of Nicolaus Copernicus in Toruń between 2001 and 2010, because of clinical suspicion of insulinoma: weakness, sweating, blured vision, confusion and dizziness.

They all were subjected to a 72-hour-fasting test, which is considered as the gold standard to recognize insulinoma. Also the imaging research of localization were performed.

The 72-hour-fasting test started at 6.00 pm. During the test patients were allowed to drink only calorie-free drinks.

We observed, in the time of a prolonged fasting test, clinical symptoms of hypoglycemia such as: central nervous system disorders, sweating, weakness, palpitations etc. If clinical symptoms of neuroglycopenia occurred, a venous blood sample was taken and plasma glucose, insulin, pro-insulin and C-peptide were measured at the time of the episodes. Fasting plasma pro-insulin, insulin and C-peptide were investigated by means of ELISA test. If plasma glucose levels were below 40 mg/dl (2.2 mmol/l) and the level of serum insulin was elevated over 6 μIU/ml, proinsulin over 5 pmol/l or C-peptide > 0.6 ng/ml, we were able to set a proper diagnosis.

Patients who were prescribed sulfonylurea derivatives or insulin, patients with critical illness, renal and hepatic failure, hipocorticoidism and sepsis were excluded from our study.

RESULTS

In our study the Whipple's triad (neurologic symptoms of hypoglycemia, blood glucose levels less than 40 mg/dl and immediate alleviation of symptoms after glucose ingestion) was present only in ten of 74 patients (8 females and 2 males). The Whipple's triad occurred within 48 hours in all except one (tab. 1). Two patients had a factitious hypoglycemia, because of insulin application. An average age of the patients with recognized insulinoma was estimated as 46.5 (females – 44 years, males – 56 years) (tab. 2).

Table 2. Patients characteristics.

Characteristics	Insulinoma	Non-insulinoma
Number of patients	10	64
Age	46.5 years	42.3 years
Females	8 (80%)	44 (68.75%)
Males	2 (20%)	20 (31.25%)
BMI*	26.3	21.8

*BMI – Body Mass Index

The imaging research of localization were performed in all of them. We implemented ultrasonography, computed tomography, somatostatin receptor scintigraphy and endoscopic ultrasonography. Only in one of the patients with diagnosed insulinoma a single tumor (2 cm), situated on a border of head and corpus of pancreas, was localized with the use of the computed tomography. Also in two of the patients with the use of the endoscopic ultrasonography an insulinoma was recognized. The patients were operated and tumors were decorticated. Definitive proof of insulinoma in these cases was obtained from histopathology of the surgical specimen. After surgical operation, stabilization of the glycaemia, during the 24-hour profile of glucose, was noticed.

Table 1. Biochemical investigations of the insulinoma patients during the prolonged fast test.

Patients	Time hours	Glucose (mg/dl) [N ≥ 50]	Insulin (μIU/ml) [N = 0-6]	Proinsulin (pmol/l) [N = 0-5]	C-peptide (ng/ml) [N = 0-0.6]	Localization insulinoma
1	8	34	34	28	8.3	Head/corpus 2 cm – CT
2	9	24	32	16	7.7	Corpus/tail 11 mm – EUS
3	11	38	31	14	3.8	Head/corpus 13 mm – EUS
4	14	39	18	8	4.2	–
5	16	36	27	16	3.2	–
6	28	37	19	9	2.8	–
7	35	39	10	7	4.1	–
8	47	32	14	8	2.5	–
9	51	38	16	13	0.0	–
10	69	37	8	7	0.0	–

The rest of the patients did not have any abnormalities of the pancreas in non-invasive imaging techniques, such as ultrasonography, computed tomography and nuclear medicine imaging. Suitable carbohydrate diet therapy, frequent meals and diazoxide or octreotide were applied. There were not any symptoms of recurrence of complaints during a three-month follow-up period.

DISCUSSION

The incidence of insulinoma in general population is estimated as 1-4/1 million people a year (3, 5, 7). In our Department the incidence of insulinoma is nearly one case per year. It is in accordance with the existing literature. The clinical symptoms of insulinoma are the subsequent development of symptoms of hypoglycemia (3, 10).

We diagnosed the insulinoma in ten of 74 patients who underwent a prolonged fasting test, because of clinical suspicion of endogenous hyperinsulinemia.

There was a tendency for insulinoma patients to be older, more often female and to have a higher BMI than non-insulinoma patients. It was comparable to the research conducted by Van Bon et al. (7). In our study the average age of patients with confirmed insulinoma was 46.5 years comparatively to non-insulinoma patients – 42.3 years. Vaidakis et al. in theirs research observed similar results (average age at 47 years) (3, 4). In our investigation the relationship proportion between females and males was 80 to 20% and higher body mass index in insulinoma patients was recognized. All these data are in accordance with the existing literature (11-13).

In the insulinoma patients non-invasive imaging techniques like ultrasonography, computed tomography, three-phasic magnetic resonance imaging scans or nuclear medicine imaging were performed. These examination methods are helpful to locate tumors larger than 1 cm (3-5). Nevertheless over 80% of insulinomas are less than 2 cm in diameter, thereby it causes large difficulties in tumor imaging (4). Sensitivity of non-invasive imaging techniques (US, CT, MRI) average out of 20 to 60% (14). In our study only in one of the patients with diagnosed insulinoma a single tumor (2 cm) was localized with the use of computed tomography.

The endoscopic ultrasonography is a high sensitive and specific diagnostic method in localization neuroendocrinal tumors. This method enables to determine the tumor invasiveness, its blood circulation and localization of small lesions (diameter under 4 mm) (3). The insulinoma was recognized in two patients with the use of endoscopic ultrasonography.

In differentiation diagnosis we must consider also nuclear medicine imaging like somatostatin receptor scintigraphy (somatostatin receptor sst_2 and sst_5) or glucagon-like peptid-1 imaging (GLP-1) or apply positron emission tomography (PET) (4, 8, 9, 15). Unfortunately, somatostatin receptors, in particular sst_2, are insufficiently expressed in many insulinomas (5, 16). However, the world reports suggest to exchange the tectreotide to octreotide in order to increase the affinity to somatostatin receptors that enhances the sensitivity of the method.

Glucagon-like peptide-1 imaging using ^{111}In-DOTA--exendin-4 is capable to localize insulinoma *in vivo*, because of very high density in almost all insulinomas, but it is very expensive and hard to access (5, 17).

The results of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET imaging of insulinomas are disappointing, because of their low proliferative potential (18).

Treatment strategy of insulinoma is surgical removal of the tumor. A simple enucleation of the tumor is successful in over 90% of cases (4, 5). The material collected during the surgery is subjected to the histopathological examination. Up to now the criteria of distinction between benign or malignant tumors have not been created.

If we do not know the localization of the tumor, the blind distal pancreatectomy should be performed or pharmacological treatment with the application of diazoxide, somatostatin analogue, chemotherapy and radiotherapy can be used.

CONCLUSIONS

In differential diagnosis we should remember about other reasons of hypoglycemia. Drugs, mainly insulin or sulphonylurea derivatives, are the most common cause of hypoglycemia in hospitalized patients (3).

The diagnosis of insulinoma is very difficult, despite available investigative methods, and sometimes takes a lot of time from 1 month to even 30 years (on average 2 years) (13). The situation results from the lack of specific signs of insulinoma. Hypoglycemia can be present in many other diseases like conduct disorders, polineuropathy, and other endocrinological illnesses (5). In addition the relationship between above-mentioned signs and results of laboratory examinations should be proved, which is very difficult in spite of the prolonged fast test availability (15).

The prolonged fast test and positive Whipple's triad have an excellent discriminative value for the presence of endogenous hyperinsulinemia (7).

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received/otrzymano: 09.09.2013
accepted/zaakceptowano: 16.10.2013

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