Endokrynologia Polska
DOI: 10.5603/EP.2015.0041
Tom/Volume 66; Numer/Number 4/2015
ISSN 0423–104X

Congenital hyperinsulinism in Polish patients — how can we optimize clinical management?

Wrodzony hiperinsulinizm — próba optymalizacji diagnostyki i leczenia u polskich pacjentów

Marta Buraczewska[1], Ewa Szymańska[2], Agnieszka Brandt[1], Przemysława Jarosz-Chobot[3], Jolanta Sykut-Cegielska[4], Ewa Barg[5], Maciej Borowiec[6], Wojciech Młynarski[6], Małgorzata Myśliwiec[1]

[1]Medical University of Gdansk, Department and Clinic of Paediatrics, Diabetology, and Endocrinology, Gdansk, Poland
[2]Radboud University Nijmegen, Institute for Molecules and Materials (IMM), Nijmegen, The Netherlands
[3]Medical University of Silesia, Department of Paediatrics, Endocrinology, and Diabetes, Silesia, Poland
[4]Screening Department, Institute of Mother and Child, Warsaw, Poland
[5]Wroclaw Medical University, Department of Basic Medical Sciences, Wroclaw, Poland
[6]Medical University of Lodz, Department of Paediatrics, Oncology, Haematology, and Diabetology, Lodz, Poland

Abstract

Introduction: Congenital hyperinsulinism of Infancy (CHI) comprises heterogenic defects of insulin secretion with diverse molecular aetiology, histological features, severity of symptoms, and response to pharmacotherapy.
The study aimed to establish the first clinical characteristics of Polish patients with CHI and to propose a novel clinical algorithm allowing the prioritisation of genetic and radiology studies, based on patient's characteristics and response to pharmacotherapy.
Material and methods: Thirty-one patients with CHI were recruited from five reference centres in Poland. Clinical and biochemical parameters were statistically evaluated and compared to those of a control group (n = 30).
Results: CHI predisposes to increased birth weight (p = 0.004), lower Apgar score (p = 0.004), perinatal complications (74%), and neurological implications (48%). Diagnostic process and therapy were inconsistent. A trial of pharmacotherapy was applied in 21 patients (68%), and diagnostic imaging with 18F-L-DOPA PET was performed in only 3. Eighteen patients (58%) were surgically treated, including 8 infants (44%) aged less than 2 months. Depending on the type of resection, further hypoglycaemia was observed postoperatively in 50% (n = 9) and hyperglycaemia in 39% (n = 7) of cases. Based on foregoing results, a clinical algorithm was proposed.
Conclusions: Standardisation of clinical management with the use of pharmacotherapy, genetic screening, and diagnostic imaging will allow the optimisation of therapy and minimisation of treatment complications. **(Endokrynol Pol 2015; 66 (4): 322–328)**

Key words: *congenital hyperinsulinism, Diazoxide, 18-F-DOPA-PET*

Streszczenie

Wstęp: Wrodzony hiperinsulinizm (CHI) obejmuje heterogenną grupę zaburzeń sekrecji insuliny przez komórki β trzustki i charakteryzuje się zróżnicowaną etiologią molekularną, obrazem histopatologicznym, nasileniem objawów oraz odpowiedzią na leczenie farmakologiczne. Celem pracy było stworzenie charakterystyki klinicznej polskich pacjentów z wrodzonym hiperinsulinizmem oraz podjęcie próby stworzenia algorytmu diagnostyczno-terapeutycznego, umożliwiającego priorytetyzację badań genetycznych i obrazowych w zależności od obrazu klinicznego, wyników badań laboratoryjnych oraz odpowiedzi na leczenie farmakologiczne.
Materiał i metody: Do badania włączono 31 pacjentów z rozpoznaną hipoglikemią w przebiegu hiperinsulinizmu z 5 ośrodków w Polsce. Analizę danych klinicznych oraz parametrów biochemicznych pacjentów hipoglikemią odniesiono do 30-osobowej grupy kontrolnej.
Wyniki: Pacjenci z CHI charakteryzowali się znacznie wyższą masą urodzeniową (p = 0,004), niższą oceną uzyskaną w okołoporodowej skali Apgar (p = 0,004), częstszymi komplikacjami okołoporodowymi (74%) oraz powikłaniami neurologicznymi (48%). Przeprowadzona w badanej grupie diagnostyka była niespójna. U 21 pacjentów (68%) włączono leczenie za pomocą Diazoksydu, a u 3 pacjentów (9,7%) wykonano diagnostykę obrazową przy użyciu 18F-L-DOPA PET. Wśród 18 (58%) pacjentów leczonych chirurgicznie u 8 (44%) resekcję wykonano w wieku poniżej 2. miesiąca życia. Pooperacyjnie w zależności od typu wykonanej operacji obserwowano hipoglikemię u 50% (n = 9), a hiperglikemię u 39% (n = 7). Na podstawie uzyskanych wyników zaproponowano pierwszy w Polsce algorytm diagnostyczno-terapeutyczny.
Wnioski: Ujednolicenie schematu postępowania diagnostycznego-terapeutycznego z wykorzystaniem wszystkich dostępnych metod umożliwi zapobieganie kolejnym epizodom choroby, oraz zminimalizuje komplikacje wynikające z leczenia.
(Endokrynol Pol 2015; 66 (4): 322–328)

Słowa kluczowe: *wrodzony hiperinsulinizm; Diazoksyd; 18-F-DOPA-PET*

Statement of financial support: Project partially financed by the Polish Diabetes Association.

Marta Buraczewska M.D., Ph.D., Department and Clinic of Paediatrics, Diabetology, and Endocrinology, Medical University of Gdansk, Dębinki St. 7, 80–952, Gdansk, Poland, phone: +48 58 349 28 15, fax: +48 58 349 28 24, email: mburaczewska@gumed.edu.pl

Introduction

Congenital Hyperinsulinism of Infancy (CHI) is the most common cause of permanent hypoglycaemia in children. It comprises a heterogenic group of insulin secretion defects, and it is characterised by diverse molecular aetiology, histological features, severity of symptoms, and response to pharmacological treatment [1–3].

Diagnosis and therapy of CHI is one of the most difficult aspects of contemporary endocrinology and diabetology. Although it is relatively easy to establish this clinical diagnosis, the management consists of many problems and pitfalls in daily care.

Symptoms of hypoglycaemia are diverse, from completely unnoticeable or very subtle to severe attacks causing irreversible damage in the central nervous system [2]. Diagnosis of CHI includes clinical assessment, laboratory tests, genetic studies, and nuclear imaging [2].

Laboratory diagnostic criteria include hypoketotic hypoglycaemia (below 45 mg/dL, 2.6 mmol/L) with detectable serum insulin level. There are no normal limits for blood insulin level. The "Normal" insulin level for normoglycaemia is usually abnormal in the presence of hypoglycaemia [4]. Required high intravenous glucose infusions (> 8 mg/kg/min, normal range 4–6 mg/kg/min) are also typical for insulin secretion defects.

A trial of diazoxide treatment and clinical observation of glucose level is the first stage of CHI management, and its result should influence further therapeutic decisions. CHI responding to pharmacotherapy with diazoxide requires no further investigations, while in the drug-resistant type genetic analysis and radiology imaging should be considered.

Molecular analysis introduced in the last decade has revolutionised diagnosis and clinical care of CHI [3, 5, 6]. In many centres identification of the genetic background of CHI has become strategic in planning further therapy: conservative treatment or radical surgical resection. Detection of particular mutations and phenotypes indicates the expected response to pharmacotherapy, morphology of pancreatic lesions (diffuse or focal forms), and allows introduction of the optimal type of surgical treatment. Mutations in eight genes (*ABCC8, KCNJ11, GLUD1, GCK, HNF4A, HADH, SLC16A1*, and *UCP2*) have been described as related to CHI. Mutations in these genes are usually recognised in 50–80% of patients, depending on the screened population and the applied genetic methods [3, 7–9]. In the remaining 20–50% of patients the genetic cause of hypoglycaemia is still unknown [1, 7]. Unfortunately, molecular studies are not fully available in Poland at the moment.

Imaging with use of 18F-DOPA PET, introduced to medical practice in the year 2003, complements molecular studies and allows differentiation between focal and diffuse forms of CHI.

In Poland there are as yet no national guidelines for clinical management of CHI. Diagnosis and therapy is based solely on physicians experience and international literature. In the study we aimed to analyse a Polish cohort with CHI and to propose a current diagnostic algorithm in order to optimise medical care of CHI.

Material and methods

In the study 31 patients with hypoglycaemia with hyperinsulinism were recruited from five diabetology, endocrinology, and metabolic centres in Poland. Analysis included patients diagnosed with CHI in the years 2000–2012.

A control group (n = 30) without hypoglycaemia, diabetes mellitus, or other carbohydrate metabolism disturbances was selected from healthy patients, in which the exact diagnostic process as in hypoglycaemia patients was applied. Patients recruited to the control group were admitted to hospital with hypoglycaemia suspicion due to general, unspecific complaints such as general malaise, poor appetite, or fainting episodes. In these patients, after detailed assessment no hypoglycaemia was noted. This group was slightly older compared to the CHI group, due to an insufficient number of patients at the age of infancy allowing us to perform the planned diagnostic process. Hypoglycaemia, diabetes mellitus, and other carbohydrate metabolism disturbances were excluded in the control group.

The following aspects were analysed: clinical characteristics of CHI patients, perinatal history, biochemical parameters, applied diagnostic tools, treatment, and complications. Diagnostic criteria for CHI included: nonketotic hypoglycaemia (< 45 mg/dL) with detectable serum insulin concentration, increase of glucose level (> 30 mg/dL) during glucagon stimulation test, and required intravenous glucose infusion rate > 8 mg/kg/min. The performed controlled fasting test lasted, depending on the age at diagnosis, from 8 (< 6 months old) to 24 hours. In 8 patients no prolonged (> 8 hours) fasting studies were performed because severe hypoglycaemia occurred during normal feeding regime (Table I).

Statistical analysis was performed with MATLAB R2013a software. It included Fisher test, Manna-Whitney U test, *t*-Student test, hierarchical cluster analysis, and Spearman correlation rank.

Table I. *General characteristics of patients with hypoglycaemia and the control group*

Tabela I. *Ogólna charakterystyka pacjentów z hipoglikemią oraz grupy kontrolnej*

Clinical parameter	CHI patients (n = 31)	Control group (n = 30)
Male	n = 12 (39%)	n = 13 (43%)
Female	n = 19 (61%)	n = 17 (57%)
Mean age at the time of clinical investigations [months]	11.8 ± 33 (0–168)	95.3 ± 61 (6–190)
Mean lowest serum glucose level [mg/dL]	17.3 ± 8.1 (4–36)	67.6 ± 9,2 (49–80)
Hypoglycaemia symptoms	n = 31 (100%)	n = 0 (0%)
Family history of hypoglycaemia	n = 7 (23%)	n = 0 (0%)
Parental consanguinity	n = 0 (0%)	n = 0 (0%)
Perinatal hypoglycaemia	n = 23 (74%)	n = 0 (0%)

Results

Clinical characteristics of patients with chi

Hypoglycaemia was observed in 87% of patients either just after birth (n = 23, 74%) or in the first year of life (n = 4, 13%). The mean lowest glucose level was 17.3 ± 8.1 mg/dL (range 4-36 mg/dL). The most common symptoms included loss of consciousness (n = 25) and seizures (n = 24) (Fig. 1).

Based on Fisher test, neither age (p = 0.1) nor serum glucose level (p = 0.2) influenced particular symptoms of hypoglycaemia.

Observed neurological complications in patients with CHI included epilepsy (n = 13, 42%), developmental delay (n = 9, 29%), and microcephaly (n = 2, 6%), while in only one patient from the control group a mild form of epilepsy was diagnosed. In patients presenting with seizures, a not statistically relevant tendency to subsequent epilepsy and developmental delay was observed. No correlation between age of first hypoglycaemia symptoms and neurological complications was observed.

Perinatal history

Patients with CHI (n = 24, 77%), as in the control group (n = 21, 70%), were usually born at term. In hypoglycaemia patients 10% were born by caesarean section compared to 7% in the control group. In 23 of CHI patients (74%) hypoglycaemia was noted immediately after birth, mainly as seizures or hypotonia (Fig. 2). In the control group no hypoglycaemia was noted after birth. Statistical analysis revealed that patients with CHI received significantly lower Apgar score in comparison to the control group (p = 0.004).

Further analysis showed higher birth weight in CHI patients (3850 ± 725 g) compared to the control group (3306 ± 641 g) (p = 0.004).

In 16 patients (52%) with hypoglycaemia foetal macrosomy was noted, compared to 5 patients (16%) from the control group (p = 0.034).

Subsequent analysis showed no correlation between birth weight and perinatal hypoglycaemia (p = 0.45).

In CHI patients with increased birth weight a tendency towards higher insulin level (33.75 ± 23.4 ulu/mL) as well as C-peptide level (3.81 ± 2.17 ng/dL) was observed. However, these trends were not statistically relevant (p = 0.1, p = 0.47, respectively).

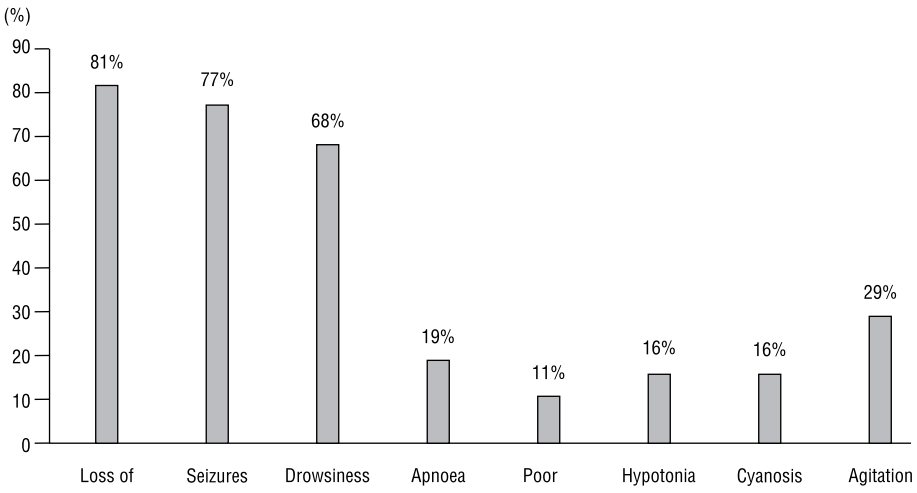

Figure 1. *Observed hypoglycaemia symptoms*

Rycina 1. *Obserwowane objawy hipoglikemii*

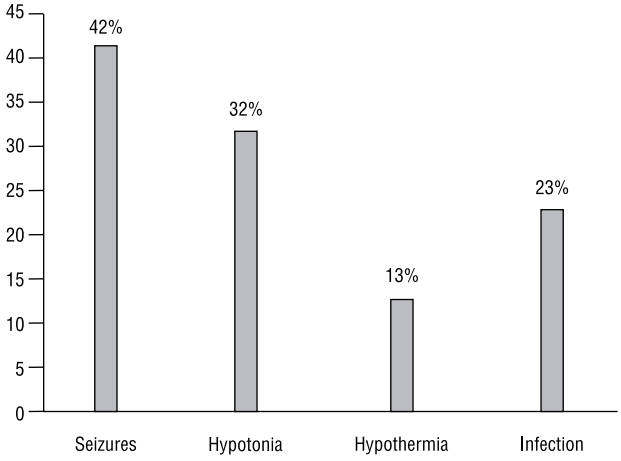

Figure 2. *Perinatal complications in CHI patients and in the control group*

Rycina 2. *Komplikacje okołoporodowe u pacjentów z CHI oraz w grupie kontrolnej*

Biochemical parameters

In CHI patients lower HbA1c and higher C-peptide and ammonia levels were observed. In 5 patients with CHI the ammonia level was higher than 100 ug/dL (range 100–273 ug/dL). There was no difference between total cholesterol or triglyceride levels.

Prolonged fasting studies showed higher lactic acid and lower pH level at the end of the test (Table II).

Correlation analysis based on Spearman's rank correlation coefficient revealed a positive correlation between fasting insulin and C-peptide levels ($R = 0.72$, $p = 0.005$). In addition, a negative correlation between fasting glucose and triglycerides levels ($R = –0.83$, $p = 0.01$) was observed.

Diagnosis and treatment

Molecular imaging with use of 18-F-DOPA-PET was performed in only three CHI patients (9.7%). Diffuse form was diagnosed in two patients, while a focus in the pancreatic head was observed in one patient.

A trial of diazoxide treatment was applied in 21 patients (68%). In the remaining 10 patients no diazoxide was applied due to problematic access to medication and precipitous decision on surgical management. Good clinical response (no further hypoglycaemia) was observed in nine patients (43%), and no other treatment was applied. Insufficient response to pharmacotherapy was observed and surgical treatment was applied in 12 patients (57%) treated with diazoxide. Surgical treatment was also applied to 6 of the 10 remaining patients not treated with diazoxide.

Besides diazoxide, offered pharmacotherapy included octreotide (n = 8, 26%), GlucaGen (n = 10, 32%), and steroids (n = 4, 13%).

A diet based on low glycaemic index as well as frequent feeding regime was introduced in 27 patients (87%). 74% of patients (n = 23) required nighttime feeding in order to prevent further hypoglycaemia.

Surgical treatment was applied in 18 patients (58%). At the time of pancreatic resection the mean age of the patients was 10.5 months (range 1–54 months, SD = 16.8 months). However, surgery was performed at age of two months or less in eight patients (44%).

Subtotal pancreatectomy was performed in 16 patients (89%), although in 2 patients subsequent total pancreatectomy was required due to persistent hypoglycaemia, despite primary subtotal resection. In one patient selective focal resection was applied and in another one partial resection was performed. Analysis of postoperative histopathological descriptions revealed diffuse forms in nine patients (50%) and focal forms in three patients (17%). In three patients the morphological picture was described as diffuse form with intensification in particular parts of pancreas, and in the three remaining patients the description was unclear.

Clinical complications, depending on the type of resection, included: further hypoglycaemia (n = 9, 50%), hyperglycaemia (n = 7, 39%), and postoperative infection (n = 2, 11%). In four patients (22%) postoperative insulin therapy was required, and in five (28%) cases enzyme replacement therapy was needed. In a patient with focal resection no postoperative complications were observed (Table III).

Discussion

Congenital hyperinsulinism most commonly occurs in the newborn period; however, it can also be observed in older children [2, 7, 10, 11]. Particularly in newborns hypoglycaemia symptoms can be very unspecific and difficult to observe. In the studied cohort mainly neurological symptoms of hypoglycaemia were observed; however, also atypical symptoms such as apnoea, cyanosis, or poor feeding occurred. Nearly half of the studied newborns were macrosomic at birth due to increased insulin activity in foetal life, which also influenced more traumatic birth history and poor Apgar score compared to healthy controls.

The characteristic metabolic profile observed during the performed diagnosis results from increased anabolic insulin activity [2, 10]. The observed strong correlation between insulin level and C-peptide confirms the diagnostic applicability of C-peptide measurements in CHI patients. Increased lactic acid level and decreased pH due to increased patient distress at the end of the study cast some doubt on the usefulness of these parameters in CHI diagnosis [7, 12, 13].

Table II. *Biochemical parameters in CHI patients and in the control group*
Tabela II. *Parametry biochemiczne u pacjentów z CHI oraz w grupie kontrolnej*

Parameter/studied group	CHI patients (n = 31)			Control group (n = 30)			
	Mean	Median	Range	Mean	Median	Range	p
HbA1c (%)	4.77 ± 0.47	4.91	4–5.43	5.33 ± 0.32	5.38	4.56–5.94	0.0078
Fasting C-peptide [ng/dL]	3.13 ± 2.19	3.12	0.5–5.74	1.13 ± 0.67	0.91	0.31–3.03	0.0007
Fasting glucose [mg/dL]	42.38 ± 21	38	19–87	77.97 ± 8.62	78.5	54–94	0.0000
Fasting insulin [ulU/mL]	24.62 ± 21.99	22	2.3–82	4.34 ± 2.99	3.4	0.5–10	0.0003
Prolonged fasting study — end of test:							
Glucose [mg/dL]	30.62 ± 13.85	31	4–64	68.93 ± 10.57	72	49–88	0.0000
Insulin [ulU/mL]	15.09 ± 17.14	7.20	2.2–79	2.76 ± 2.47	1.75	1–10.1	0.0000
pH	7.35 ± 0.06	7.37	7.2–7.46	7.39 ± 0.04	7.39	7.3–7.45	0.0070
Lactic acid [mg/dL]	14.09± 16.75	9.7	0.9–56	2.16 ± 0.75	2.3	1–3.4	0.0003
Ammonia [ug/dL]	106.77 ± 72.29	93	23–273	33.10 ± 10.95	28	22–44	0.0003
Free fatty acids [mmol/L]	0.68 ± 0.85	0.34	0.05–3.7	0.7 ± 0.43	0.69	0.01–1.51	0.2792
Lipids:							
Triglycerides [mg/dL]	82.94 ± 52.78	67	22–224	68.93 ± 29.97	66.00	33–185	0.7619
Total cholesterol [mg/dL]	161.8 ± 40.04	158	86–266	163.71 ± 30.17	162.50	112–253	0.6429

Table III. *Postoperative complications in patients with CHI depending on type of surgery*
Tabela III. *Komplikacje pooperacyjne u pacjentów z CHI w zależności od typu operacji*

Complications	Total resection (n = 2)	Partial resection (n = 1)	Subtotal resection (n = 14)	Focal resection (n = 1)
Hyperglycaemia	n = 2	n = 0	n = 5	n = 0
Insulin therapy	n = 2	n = 0	n = 2	n = 0
Enzyme replacement	n = 2	n = 0	n = 5	n = 0
Infection	n = 0	n = 0	n = 2	n = 0
Hypoglycaemia	n = 0	n = 1	n = 8	n = 0

The strong negative correlation between fasting glucose level and serum triglycerides supports the expected negative effect of increased feeding frequency and increased simple carbohydrates intake in CHI patients.

Assessment of clinical response to pharmacological treatment is crucial in management of congenital hyperinsulinism [2]. The introduction of diazoxide in CHI therapy is the first-line treatment and determines further clinical management.

Our study confirmed that in nearly half of patients a positive clinical response to diazoxide is observed [1, 11]. Unfortunately, contrary to American and French observations [1, 7], a lack of therapy in 32% of the described patients is reported. Moreover, in six patients surgical treatment was applied with no preceding diazoxide therapy due to unknown reasons.

Pancreatic surgery was performed mainly in the first year of life. Moreover, in 44% of patients surgery was performed in the first two months of life, which could be an insufficient period for clinical observation and exclusion of transient forms [4].

Radiology imaging with use of 18-F-DOPA-PET was introduced into clinical practice in Poland in 2003. The available refund of this test by National Health Board has become an additional advantage over molecular studies.

For many years surgical treatment was based exclusively on total or subtotal pancreatectomy [14–16]. Currently, new diagnostic tools introduced into clinical practice enable the application of other, less traumatic types of surgical treatment [14, 17]. Subtotal pancreatic resection causes many complications, including hypo- and hyperglycaemia, whereas in focal resection all observed symptoms subside and no complications are observed.

In spite of increasing knowledge on pathogenesis and treatment of CHI, paediatricians, diabetologists,

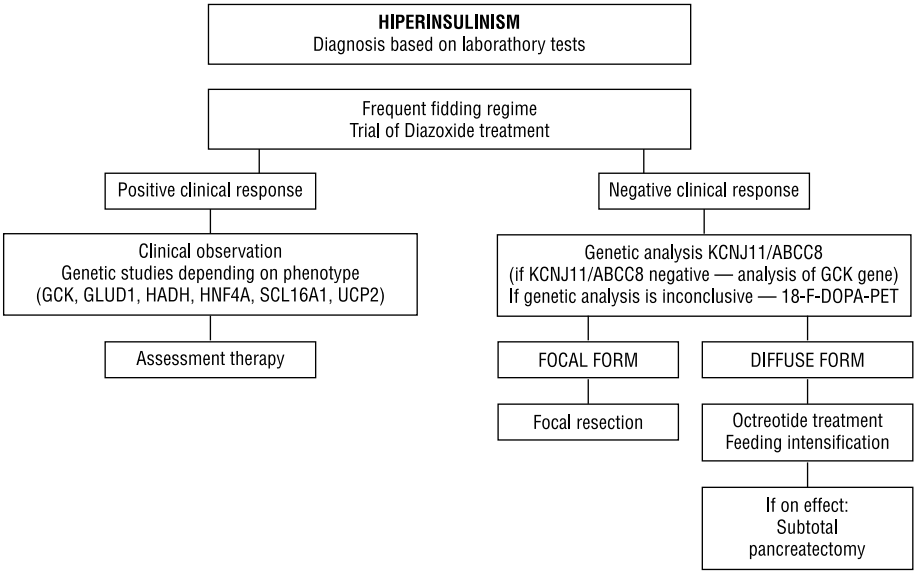

Figure 3. *Proposed clinical algorithm of management of CHI*

Rycina 3. *Propozycja algorytmu diagnostyczno-terapeutycznego u pacjentów z CHI*

and endocrinologists still have to make difficult clinical decisions. The applied treatment, in effect, may lead to other long-term complications such as diabetes.

Depending on the available diagnostic tools various schemes of diagnostics and treatment of CHI are applied in different centres. So far there are no clinical guidelines on the management of CHI available in Poland. CHI diagnosis in a Polish cohort may be further improved by recently introduced molecular studies (Medical University of Lodz, Jagiellonian University in Krakow, Medical University of Gdansk).

Below we present a proposal of a diagnostic algorithm of CHI (Fig. 3).

After laboratory confirmation of hyperinsulinaemic hypoglycaemia (nonketotic hypoglycaemia < 45 mg/dL or < 2.6 mmol/L with detectable insulin level), frequent feeding regime and clinical observation of transient forms for minimal time of two months is required [7]. Following that, the trial of diazoxide treatment should be applied. Treatment usually lasts for five days in order to assess the clinical response (glycaemia > 55 mg/dL or > 3 mmol/L despite normal diet or prolonged fasting). In patients with good clinical response further observation is usually sufficient. In patients not responding to diazoxide further diagnosis based on molecular studies and 18-F-DOPA-PET should be performed. 18-F-DOPA-PET is currently more accessible than genetic analysis in Poland; however, if genetic studies are available we recommend to do this first as it is less invasive. Genetic studies include the genes *ABCC8, KNCNJ11*, and *GCK*. If diffuse form is confirmed in genetic analysis, no further imaging is needed. Focal forms require an additional PET scan (to describe its localisation) and limited pancreatectomy.

In diffuse forms intensification of feeding and pharmacotherapy with somatostatin analogues should be applied. In the most severe cases total or subtotal resection should be performed.

Conclusions

In the study we presented the first analysis of phenotype, diagnosis, and treatment of Polish patients with congenital hyperinsulinism. CHI predisposes to increased birth weight and perinatal complications, and may lead to permanent brain injury. A diagnostic process of CHI is essential in further therapy, and the applied treatment influences subsequent complications. So far, diagnosis and therapy of congenital hyperinsulinism in Poland has been inconsistent.

Standardisation of hypoglycaemia management with the use of all available methods including pharmacotherapy, molecular imaging, and genetic analysis will allow the prevention of subsequent hypoglycaemia episodes and will minimise treatment complications. We believe that the proposed clinical algorithm will contribute to optimisation of medical care and prevent unnecessary subtotal or total pancreatic resections leading to irreversible physical disability.

References

1. Stanley CA, Matschinsky FM. Historical Perspective on the Genetic Forms of Congenital Hyperinsulinism. In: Stanley CA, De Leon DD (eds.). Monogenic Hyperinsulinemic Hypoglycemia Disorders. Front Diabetes. Basel, Karger 2012; 21: 1–6.
2. Mohamed Z, Arya VB, Hussain K. Hyperinsulinaemic Hypoglycaemia: Genetic Mechanisms, Diagnosis and Management. J Clin Res Pediatr Endocrinol 2012; 4:169–181.
3. Sneider KE, Becker S, Boyajian L et al. Genotype and Phenotype Correlations in 417 Children With Congenital Hyperinsulinism. J Clin Endocrinol Metab 2013; 98: 355–363.
4. Hussain K. Diagnosis and Management of Hyperinsulinaemic Hypoglycaemia of Infancy. Horm Res 2008; 69: 2–13.
5. Banerjee I, Avatapalle B, Padidela R et al. Integrating genetic and imaging investigations into the clinical management of congenital hyperinsulinism. Clin Endocrinol 2013; 78: 803–813.
6. Senniappan S, Shanti B, James C et al. Hyperinsulinaemic hypoglycaemia: genetic mechanisms, diagnosis and management. J Inherited Metabolic Disease 2012; 35: 589–601.
7. Arnoux JB, Verkarre V, Saint-Martin C et al. Congenital hyperinsulinism: current trends in diagnosis and therapy. Orphanet J Rare Dis 2011; 63: 1–14.
8. Flanagan SE, Damhuis A, Banerjee I et al. Partial ABCC8 gene deletion mutations causing diazoxide-unresponsive hyperinsulinaemic hypoglycaemia. Ped Diab 2012; 13: 285–289.
9. Flanagan SE, Clauin S, Bellanné-Chantelot C et al. Update of mutations in the genes encoding the pancreatic β-cell K(ATP) channel subunits Kir6.2 (KCNJ11) and sulfonylurea receptor 1 (ABCC8) in diabetes mellitus and hyperinsulinism. Hum Mutat 2009; 30: 170–180.
10. Aynsley-Green A, Hussain K, Hall J et al. Practical management of hyperinsulinism in Infancy. Arch Dis Child Fetal Neonatal Ed 2000; 82: 98–107.
11. Sogno Valin P, Proverbio MC, Diceglie C et al. Genetic Analysis of Italian Patients with Congenital Hyperinsulinism of Infancy. Horm Res Paediatr 2013; 79: 236–242.
12. Arnoux JB, de Lonay P, Ribeiro M J et al. Congenital hyperinsulinism. Early Hum Dev 2010; 86: 287–294.
13. Kapoor R, Flenegan SE, Arya VB et al. Clinical and molecular characterisation of 300 patients with congenital hyperinsulinism. Eur J Endocrinol 2013; 168: 557–564.
14. Beltrand J, Caquard M, Arnoux JB et al. Glucose Metabolism in 105 Children and Adolescents After Pancreatectomy for Congenital Hyperinsulinism. Diabetes Care 2012; 35: 198–203.
15. Lovvorn HN, Nance ML, Ferry RJ et al. Congenital hyperinsulinism and the surgeon: lessons learned over 35 years. J Pediatr Surg 1999; 34: 786–792.
16. Shilyansky J, Fisher S, Cutz E et al. Is 95% pancreatectomy the procedure of choice for treatment of persistent hyperinsulinemic hypoglycemia of the neonate? J Pediatr Surg 1997; 32: 342–346.
17. Jack MM, Walker RM, Thomsett MJ et al. Histologic findings in persistent hyperinsulinemic hypoglycemia of infancy: Australian experience. Pediatr Dev Pathol 2000; 3: 532–547.