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Short-term Outcomes of Pancreatectomy in Congenital Hyperinsulinism: A Retrospective Multi-center Study

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ABSTRACT

Background: Congenital hyperinsulinism (CH) is a well-known cause of the persistent neonatal hypoglycemic state that may lead to irreversible neurological damage. While medical therapy can improve the condition in some cases, refractory cases require further investigation to identify focal or diffuse pancreatic lesions. Surgery is the main treatment for refractory cases and can improve the neurological and glycemic status of patients. The study aimed to evaluate the short-term outcomes of surgical intervention in cases of CH who underwent surgical treatment.

Methods: A multicenter cross-sectional survey was conducted to review cases of CH that underwent surgery between 2018 and 2020. Focal cases were treated with simple enucleation or distal pancreatectomy, while diffuse cases underwent near-total pancreatectomy. The glycemic and neurological states of the patients were evaluated and the results were analyzed.

Results: Among the 56 neonates who underwent pancreatic surgery, 48 (85%) had diffuse disease, and the remaining cases suffered from focal lesions. All focal cases achieved normoglycemia, while 24 (50%) of the diffuse cases achieved normal glycemic levels (P≤0.003). Additionally, the incidence of irreversible neurological deficits was higher in the diffuse group (P=0.029).

Conclusion: The focal form of CH seems to be totally curative by surgical operations. However, the proper management of diffuse form is still demanding. Although in our study, we had an acceptable success rate in the short-term, lifelong euglycemia may not be obtainable in these patients.

Keywords: Congenital hyperinsulinism, Neonates, Neurologic disorder, Pancreatectomy

Introduction

Congenital Hyperinsulinism (CH) is a rare genetic disorder that affects the regulation of insulin secretion in newborns. It is the main cause of refractory hyperglycemia, a condition where blood sugar levels remain high despite medical treatment. The dysregulated secretion of insulin from pancreatic β-cells in CH leads to persistent hypoglycemia, which can manifest as signs and symptoms of a hypoglycemic state, such as irritability, seizures, lethargy, and poor feeding (1). The outcomes of CH can be severe, and early diagnosis and prompt management are essential to prevent long-term complications. In addition to the acute complications of persistent

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hypoglycemia, CH is also associated with long-term neurological issues, developmental delays, and even lifelong brain damage. This is because the brain is particularly sensitive to low blood sugar levels, which can cause irreversible damage if left untreated (2).

Clinicians have described two distinct types of the disease based on their clinical manifestations and outcomes: diffuse and focal forms, each with similar genetic characteristics (3).

Near-total resection of the pancreas is the treatment of choice in patients with a diffuse pattern, and this procedure usually is associated with further diabetes or impaired blood glucose. Conversely, focal lesions tend to have better outcomes and require less invasive surgical procedures (4).

Despite successful surgical interventions in these cases, a notable proportion of patients develop disturbed glycemic states. A considerable percentage of diffuse cases may experience diabetes mellitus due to the extensive loss of pancreatic cells during surgery. Moreover, inadequate resection of pancreatic lesions may lead to continuous persistent hypoglycemia postoperatively. Additionally, some cases may experience irreversible neurological and developmental deficits (5).

Despite undergoing proper surgery, the outcomes of CH have been less than desirable. Therefore, we conducted a retrospective survey to analyze our experience in managing CH in neonates and evaluate the outcomes. The purpose of the study was to evaluate the outcomes of surgical intervention in cases of CH. Specifically, the study aimed to compare the effectiveness of surgical treatment between focal and diffuse cases of the disease in achieving normoglycemia and improving neurological status.

Methods

Study design

Our study aimed to investigate the management and outcome of pancreatic surgery in patients with CH, with a specific focus on identifying factors associated with better short-term outcomes. To this end, we conducted a retrospective review and analysis of all relevant cases between February 2018 and May 2020. This study was approved by Iran National Committee for Ethics in Biomedical Research (IR.SMBUMSP.REC.1398.962).

Setting and population

The present study was performed in three prominent children's referral hospitals located in Iran (Tehran, Tabriz, and Ahwaz). We reviewed all the patients with a diagnosis of CH who underwent some kind of pancreatectomy. The definitive diagnosis was made on the basis of clinical examination, laboratory tests, and imaging studies. Besides, diagnosis suspicion was established based on abnormal serum glucose levels found during neonatal screening. Newborns who were unable to maintain preprandial plasma glucose > 50 mg/dL for 48 h with medical treatment were susceptible to persistent or refractory hypoglycemia (6, 7).

Medical management

After confirming CH, medical treatment was initiated using both oral and intravenous routes. The most frequently administered oral agent was dextrose gel. In cases where the oral intake was insufficient to maintain normoglycemia, intravenous dextrose infusion was initiated (8). Long-term medical management consisted of using diazoxide, chlorothiazide, and glucagon (1). In addition to accurate medical therapy, finding the predisposing genes was another objective. Patients who failed to tolerate the medical treatment or had unsuccessful treatment were referred for surgical consultation.

Imaging studies

Commonly used non-invasive imaging techniques, such as transabdominal ultrasonography, computed tomography (CT) scan, and magnetic resonance imaging (MRI), were employed to rule out any potential associated anomalies. Furthermore, to distinguish between focal and diffuse lesions in the pancreas, positron emission tomography (PET/CT) was utilized (9).

Operative technique

We followed a standardized institutional protocol, where all surgeries were performed by pediatric surgeons using a supraumbilical horizontal laparotomy incision in every patient. For cases involving the focal disease, the primary operation was simple enucleation or distal pancreatectomy, depending on the lesion's location. It is worth mentioning that routine splenectomy was not performed during distal pancreatectomies. For the cases of diffuse disease that failed to respond to medical treatment, subtotal or near-total pancreatectomy was performed. Near-total pancreatectomy includes the resection of the whole pancreas except a thin rim in the head of the pancreas (to avoid the

Whipple procedure). Informed consent was taken from the parents or legal guardians due to the patients' age.

Inclusion and exclusion criteria

Following the International Classification of Diseases 10th Revision, we reviewed the neonates diagnosed with CH between February 2018 and May 2020 (E16.1), and the operated cases were included in the study. Neonates who were unable to maintain preprandial plasma glucose > 50 mg/dL for 48 h with medical treatment were considered to have persistent or refractory hypoglycemia and were eligible for inclusion. Major laboratory diagnostic criteria included low fasting plasma glucose (<50 mg/dL), inappropriately increased insulin levels (>2 μU/mL), glycemic response by intravenous glucagon administration (>30 mg/dL), and glucose infusion rate required to maintain normoglycemia. Besides, in equivocal laboratory results, the measurement of blood β-hydroxybutyrate and free fatty acids was useful (10). Subsequently, only confirmed cases were chosen for surgical treatment. On the other hand, we excluded neonates who died before the surgical intervention and those who underwent operations in other medical centers and referred to our hospitals for the treatment of postoperative complications. We also restricted our analysis to neonates aged less than 30 days when CH confirmed and excluded the infants who did not receive proper medical treatment before this age. In addition, patients who denied to have surgical care in our institutes, were discharged against medical advice, and missed follow-ups were not included.

Outcomes

As there are no validated criteria or scoring systems to evaluate the curability of these patients, we only used the term "cured" for the cases who became normoglycemic after the surgery and did not develop any neurological deficits.

Data gathering and analysis

Each center's medical records were extracted by trained pediatric surgery fellows and recorded in an online collaborative spreadsheet software. Afterward, the final dataset was imported and analyzed in Statistical Package for the Social Sciences (SPSS) version 26 (IBM, Armonk, NY). For scale variables, central tendency and dispersion measures were utilized, while frequencies were computed for categorical variables. Chi-square and Fischer's tests were used to determine any association between two categorical variables. Independent t-test and one-way ANOVA were employed to compare the means of numerical values. The study found statistical significance when the p-value was less than 0.05.

Results

Preoperative information

In this study, 56 patients were enrolled from three different centers. Table 1 demonstrates that the majority of cases involved female patients (60.7%). The means for variables, such as gestational age, birth weight, and age of presentation, are also presented in Table 1. There were no significant differences in the distribution of cases across the three institutes, except for the age of presentation, which showed a statistically significant difference between the hospitals (P=0.044).

Table 1. demographics and preoperative data

Variable	Total value	Tehran	Ahwaz	Tabriz	P-value*
Gender (n, %)					0.939
Male	22 (39.3)	9 (36)	5 (41.7)	8 (42.1)	
Female	34 (60.7)	16 (64)	7 (58.3)	11 (57.9)	
Gestational age (weeks)	37±1.9	36.7±2.1	36.5±2.3	37.5±1.3	0.282
Birth weight (g)	3838±741	4070±922	3466±670	3768±311	0.057
Presentation age (days)	1.39 (1-4)	1.28 (1-3)	2 (1-4)	1.16 (1-2)	0.026
GDM** (n, %)	10 (17.9)				0.613
Insulin Level (mIU/L)	48.6±14.8	50.1±17.0	44.25±13.4	49.5±12.6	0.512
IGR†	2.1±0.9	2.26±1.1	1.89±0.51	2.21±0.7	0.511
GIR‡	13.7±1.8	14.1±2.3	13.25± 1.4	13.4± 1.2	0.301
Lesion type (n, %)					0.260
Diffuse	48 (85.7)	21 (84)	12 (100)	15 (78.9)	
Focal	8 (14.3)	4 (16)	0	4 (21.1)	

*These values show the associations between the institutes' information
**Gestational diabetes mellitus
†Insulin to glucose ratio
‡Glucose infusion rate (mg/kg/min)

Operative and postoperative data

Table 2 presents a concise overview of operative and postoperative information for all cases. The average time for surgery was 34.2 days after birth; however, the range varied widely from 15 to 71 days. Additionally, the average time for medical treatment was approximately one month. The vast majority of cases (85.7%) were classified as a diffuse type of disease, while 8 (14.3%) patients had focal lesions. Moreover, the majority of patients (85.7%) underwent near-total pancreatectomy.

Table 2. Surgical and postoperative data

Variable	Total	Focal	Diffuse	P-value
Age at surgery (days)	34.2±14.3	31.6±13.3	34.7±14.6	0.576
Medical treatment duration (days)	32.8±14.3	30.5±13.4	33.2±14.5	0.615
Surgery type (n, %)				<0.001
Near total	48 (85.7)	0	48 (100)	
Distal	5 (8.9)	3 (37.5)	0	
Enucleation	3 (5.4)	5 (62.5)	0	
Outcome (n, %)				0.003
Normoglycemic	32 (57.1)	8 (100)	24 (50)	
Hypoglycemic	11 (19.6)	0	11 (22.9)	
Diabetic	13 (23.2)	0	13 (27.1)	
Mortality (n, %)	9 (16.1)	0	9 (18.8)	0.181

Comparison of diffuse vs. focal disease

The neonates with diffuse disease had an average gestational age of 36.8±2.0, while those in the focal group had an average age of 38.1±1.1. Despite the slightly higher gestational age in the focal group, no significant difference was observed (P=0.080). Additionally, the average birth weight was lower in the diffuse group (3,768±760 g vs. 4,256±440 g); nevertheless, this difference was not statistically significant (P=0.085). However, the diffuse group had a significantly higher insulin-to-glucose ratio compared to the focal lesions (2.24±0.9 vs. 1.72±0.4, P=0.028), though there was no statistical difference in the serum insulin level (P=0.34).

A quick review of Table 2 reveals that there were no significant differences in the age of surgery or medical treatment duration. However, there were significant differences in the distribution of surgery types (P<0.001). Patients with focal lesions only underwent simple enucleation or distal pancreatectomy, while these minor surgeries were not performed in patients with diffuse disease. Children with diffuse lesions underwent the near-total pancreatectomy procedure.

Response to the surgery

We followed the children until they were two years old and measured their blood glucose and HbA1c levels every three months. All children diagnosed with focal disease maintained normoglycemia after surgery (P<0.003). However, patients with diffuse disease showed varying responses to surgery. Out of the 48 cases with diffuse disease, 24 (50%) remained normoglycemic, while the other half developed hypoglycemia or diabetes, suggesting excessive or inadequate resection.

Complications and outcome

We only observed three cases with complications (5.4%). Two patients experienced postoperative intestinal obstruction, one of whom required surgical intervention. The other complication was a surgical site infection that was treated with appropriate intravenous antibiotics.

Moreover, only two patients required reoperation. There were 9 (16.1%) mortalities in this study, and all these cases had diffuse disease. No mortality was reported in patients with focal lesions who underwent minor operations.

It should be noted that among the surviving children, 19 (40.4%) developed neurological deficits, which included developmental delay and motor, speech, and cognitive disorders. As expected, the majority of cases were from the diffuse group, and only one patient (2.1%) with a focal disease developed some level of speech sequelae.

According to the previous definition in the Method section, 51.8% of cases were considered cured. Moreover, the rate of curability was much higher in subjects with focal lesions than in those with diffuse types (87.5% vs. 45.8%, P=0.029). As the type of surgical procedure depended on the lesion type (Pearson coefficient=0.952), multivariate analysis demonstrated that the rate of curability was not associated with the surgical procedure. These investigations suggest that the main predicting factor for curability is the type of lesion. Accordingly, patients with focal lesions are more likely to become normoglycemic and neurologically healthy after surgery (Figure 1).

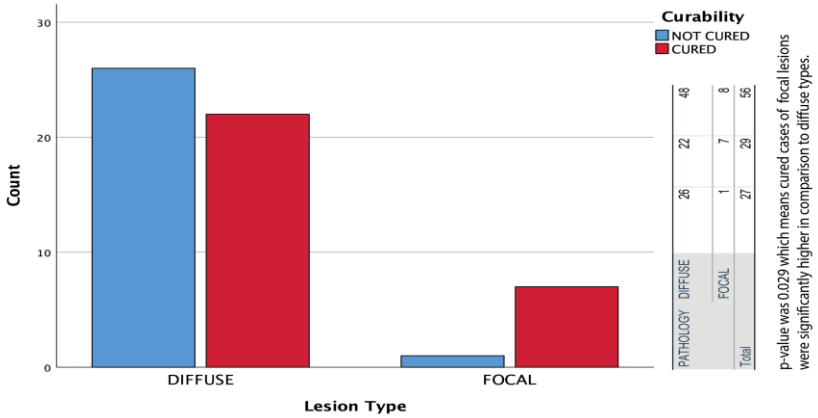

Figure 1. Rate of curability in both forms. Cured cases are those who became euglycemic after surgery, and did not develop neurological deficits

Discussion

Congenital hyperinsulinism is a rare disorder that results from dysregulated insulin secretion from pancreatic β-cells, leading to abnormal glucose metabolism. In the United States, the estimated incidence of this disorder is 1 in 50,000 (11). However, due to its rarity and limited reporting, global incidence cannot be accurately assessed.

Recently, several genes have been identified as potential genetic factors contributing to CH. These genes may affect glucose metabolism through three distinct pathways, namely dysregulation of channel and transporter proteins (e.g., ABCC8 and KCNJ11, which are the most well-known genes associated with CH), abnormalities in metabolism, and transcription factors. Mutations in KCNJ11 are only responsible for the focal form of the disease, while all other known mutations are associated with the diffuse form. However, the genetic basis of CH is still not fully understood, and further research is needed to elucidate the underlying mechanisms (12).

Despite the differences in genetic pathways, clinical manifestations are almost similar in both focal and diffuse diseases. Since CH is usually present during the neonatal period, we cannot describe any specific disease symptoms. Nonetheless, nonketotic hypoglycemia and lowered levels of serum glucose may alert physicians. Delayed diagnosis or unsuccessful treatment may lead to irrecoverable situations, such as neurological or developmental problems (13).

Diagnosis suspicion is often based on laboratory tests. Lowered plasma glucose, elevated serum insulin, and low plasma β-hydroxybutyrate may support the diagnosis. However, further laboratory investigations are necessary in equivocal cases (14). It should be noted that currently, there are no specific biomarkers available to differentiate CH, and the sensitivity and specificity of available biomarkers are not satisfactory. For this reason, additional imaging studies are performed in many tertiary centers to confirm the disease.

Although conventional imaging studies, such as transabdominal ultrasonography, CT scan, and MRI, may be useful in detecting pancreatic lesions, 18-fluoro DOPA positron emission tomography (PET/CT) is the most helpful modality for detecting focal forms of CH (9). Recently, the use of PET/CT has decreased the need for invasive diagnostic approaches, such as Arterial Stimulation with Venous Sampling and Transhepatic Portal Venous Sampling, which were utilized previously. However, the usage of these invasive methods is still necessary in challenging cases (4, 15). It should be noted that, in our reviewed cases, all the focal lesions were diagnosed by non-invasive imaging studies preoperatively. However, intraoperative palpation by experienced surgeons confirmed the extent of the lesions.

Medical treatment should be initiated promptly following the diagnosis of persistent hypoglycemia. The primary objective of medical therapy is to maintain plasma glucose levels within the desired range (>70 g/dL). This remains the mainstay of treatment even after successful surgery, as normoglycemia is critical in preventing neurological deficits and developmental issues. For this reason, both oral and intravenous glycemic products can be administered initially (16). Nevertheless, other long-acting agents, such as diazoxide, are commonly used to improve glucose metabolism in these patients (17).

Patients who respond well to diazoxide can be safely discharged with restricted blood glucose monitoring at home. However, similar to any medication, diazoxide has potential adverse effects and complications, including renal impairment, nausea, loss of appetite, and a possible risk of necrotizing enterocolitis, which both physicians and parents should be aware of. If the patient cannot tolerate medical therapy, further genetic and imaging studies must be conducted to confirm pancreatic lesions (CH) (18, 19). In diffuse forms, some tertiary centers may attempt another trial of intensive medical treatment; however, surgical intervention is considered the treatment of choice for both focal and diffuse lesions (20).

There is a global consensus on surgical management for focal disease. Although preoperative PET/CT can identify focal lesions, in challenging cases, intraoperative palpation, ultrasonography, and frozen section can help guide the surgeon's decision. A great deal of research on children estimated the success rate of pancreatectomy in focal forms of CH to be around 97% (4). In our study, all focal cases became euglycemic after surgery, which is consistent with the success rate reported in the aforementioned study. However, as stated in the Methods section, the term "cured" in our study refers to achieving a euglycemic state without any neurocognitive sequelae. With this definition, 7 (87.5%) infants in our cases were considered cured.

On the other hand, the management of diffuse forms still presents a challenge. Some tertiary centers recommend intensive medical treatment trials with somatostatin analogs, such as octreotide and lanreotide, while others suggest a near-total pancreatectomy without any delay (21). Children who fail to respond to medical therapy will likely require surgical treatment. A near-total pancreatectomy (98%) and gastrostomy tube placement may be reasonable options for these patients. However, it is important to note that this surgery is considered palliative, and the majority of cases will continue to experience hypoglycemia or diabetes (22).

Additionally, our study evaluated the short-term outcomes of pancreatectomy. A study on 105 cases who underwent near-total pancreatectomy reported that almost all (100%) of these children experienced hyperglycemia by age 13 (23). However, in our short-term follow-up, approximately 50% of our cases exhibited euglycemia.

Finally, it is important to acknowledge that, similar to any other study, our research had some limitations. The most prominent concern was the duration of follow-up. We monitored the infants for two consecutive years, which is not a significant time frame for evaluating the outcomes of near-total pancreatectomies. Additionally, another limitation was the lack of standardized scoring systems for assessing the curability of patients following surgery.

Conclusion

Surgical operations appear to provide a complete cure for the focal form of CH. However, the management of the diffuse form remains challenging. Although our study reported an acceptable success rate in the short term, it is important to note that achieving lifelong euglycemia may not be attainable for these patients.

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None.

Conflicts of interest

The authors declare that they have no conflict of interest.

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