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Patterns of Islet Cell Dysmaturation Syndrome among Saudi Infants

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Abstract. Islet cell dysmaturation syndrome is the most common cause of hypoglycemia in early infancy. A retrospective study patterns of Islet cell dysmaturation syndrome among infants presenting with hypoglycemiais on 28 patients from 2007-2011, follow-up mean 12.8 ± 6.8 months, was conducted. Diagnosed based on high intravenous glucose requirement, high insulin/glucose ratio, negative urinary ketones, and duration of repeated episodes of hypoglycemia more than 6 months. Enrolled patients underwent neurological assessment, both radiological and electrophysiological. Patients who failed medical therapy underwent near-total pancreatectomy. Transient hypoglycemia of infancy found in 16 patients 57% and islet cell dysmaturation syndrome in 43%. Eight of them presented with hypoglycemic seizures. Most of the cohort required near-total pancreatectomy 58.3%. Three pancreatectomized patients developed insulin-dependent diabetes mellitus. Two medically treated patients developed insulin-dependent *diabetes mellitus* and weight gain. The majority (91.7%) was followed-up to at least 1 year of age (follow-up was 14.8 ± 6 months). Four suffered from repeated hypoglycemic seizures during follow-up. Early intervention is necessary to avoid neurological damage. Surgically and medically treated patients are at risk of developing insulin-dependent *diabetes mellitus.* Morbidity in survivors of Islet cell dysmaturation syndrome is high and calls for greater awareness, early diagnosis and genetic counseling.

Keywords: Islet cell dysmaturation syndrome, Hyperinsulinemia; hypoglycemia, Transient hypoglycemia of infancy management.

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Introduction

Islet cell dysmaturation syndrome (ICDS), also known as persistent hyperinsulinemic hypoglycemia of infancy (PHHI) and formally known as nesidioblastosis, is a disorder of glucose metabolism characterized by inappropriate insulin secretion and profound hypoglycemia[1]. Hypoglycemia of infancy can be either transient or persistent[2]. Transient hypoglycemia of infancy usually resolves within 6 month of its onset and rarely requires medical intervention. The incidence of ICDS in general has been reported to be lower than that in the Kingdom of Saudi Arabia, 1:50,000 *vs.* 1:2500 per live births, respectively. This is mainly due to the high prevalence of consanguinity in Saudi Arabia, which lead to an increase in familial cases of ICDS in contrast to the general population where most cases are sporadic[3,4]. However, this very high incidence in Saudi Arabia, 20 times more than other part of the world as quoted in more than 200 papers in the English literature, neither substantiated by the number of cases in reported studies from Saudi major medical centers. Whether as single or multicenter, in short or long term cumulative follow up studies[6-10] nor observed in our clinical practice over the last 30 years.

Insulin, which is secreted from the pancreatic β-cells, is controlled by the K_{ATP} channels. Two proteins play a major role in the balance of the K_{ATP} channels; these proteins are coded for by the sulfonylurea receptor gene and the inward rectifying potassium channel subunit gene. It has been reported that anomalies of these genes is recognized in less than 60% of patients with ICDS, which explained inappropriate release of insulin by the β-cells[11,12]. Familial forms may be caused by several recessive or dominant genetic defects, including the sulfonylurea receptors (SUR1) gene[11]; the potassium inward rectifying receptors (Kir6.2) gene[12]; the glutamate dehydrogenase gene[13] and the glucokinase gene[14]. ICDS is the most common cause of hypoglycemia in early infancy. It requires both, early and aggressive treatment to prevent irreversible brain damage[15-17]. Management modalities of this syndrome mainly are high glucose infusion and a high calorie diet, medical therapy with diazoxide, which is not always effective especially in familial cases, somatostatin analogues (octreotide) or both. When all other options had been exhausted then surgical intervention (near-total pancreatectomy) is required[18].

In the presented study, it describes the patterns of ICDS among Saudi infants presenting with hypoglycemia at King Abdulaziz University (KAU) Hospital, and reporting our experience in medical and surgical management of patients with hyperinsulinmic hypoglycemia.

Methodology

This is a prospective study conducted on 28 children (7 girls and 21 boys) at KAU Hospital in Jeddah, Saudi Arabia, who presented with hypoglycemia between 2007 and 2011. Overall mean and standard deviation (SD) of the follow-up period were 12.8 ± 6.8 months, respectively (ranging from 2 to 30 months). Infants with other forms of hypoglycemias with specific metabolic / endocrine derangements or hyperinsulinism associated with specific syndromes like Beckwith's or familial adenomatosis were excluded. Detailed history regarding the onset, duration and nature of hypoglycemic episodes and all details of birth history, family history, sibling affection and consanguinity, as well as physical examination findings were recorded.

Islet cell dysmaturation syndrome (ICDS) was diagnosed based on high intravenous glucose infusion ≥ 12 mg/kg/minute, insulin to glucose ratio ≥ 0.3, 30 minute-glucose increment ≥ 30 mg/dL (1.67 mmol/L) in response to 0.5 mg intramuscular glucagon, and negative urine ketones. Transient hypoglycemia of infancy was defined as hypoglycemia that begins during infancy recurring over period of less than 6 months, and resolving spontaneously without the need for somatostatin analogues or surgery. Growth hormone (GH), cortisol, adrenocorticotrophic hormone (ACTH), insulin, lactate, ammonia and urinary ketones were measured during hypoglycemia. Patient neurological assessment was performed, both radiologically *via* magnetic resonance imaging (MRI) or computed tomography (CT), and electrophysiologically *via* electroencephalogram. Preoperative assessment of the pancreas performed on all patients through ultrasound and computed tomography (CT). Our management policy was to maintain blood sugar level at ≥ 60 mg/dL (3.33 mmol/L).

Medical therapy included diazoxide (maximum dose, 20 mg/kg/day) and octreotide (maximum dose, 20 mcg/kg/day) as well as intravenous glucose infusion. Anticonvulsants were used for uncontrolled seizers; mainly in those who had a delayed referral to our center, thus a delay in therapy initiation. Continuous intravenous glucagon infusion was also

used when necessary. If medical therapy as initial management failed (development of side effects or lack of response), the patient was subjected to near-total pancreatectomy (95%).

The surgical technique used began with wide upper abdominal incision. Pancreas was then approached in the bed of the lesser sac through the divided gastrocolic ligament, with the securing divided blood vessels then mobilizes the duodenum. Then, expose the head, body and tail of the pancreas (Fig. 1). In all of the patients, the pre-operative radiological ultrasound and CT scanning of the pancreas were of normal finding and intra-operative inspection, and palpation of the whole pancreas did not indicate any focal swelling or nodularity. Intra-operative biopsies were taken for frozen-section histopathology to confirm the diffuse nature of the condition. A near-total pancreatectomy (95%) in all operated patients (Fig. 2) starting pancreatic mobilization from tail to body saving the spleen was performed. Utilizing bipolar coagulation in dividing short pancreatic vessels crossing its upper

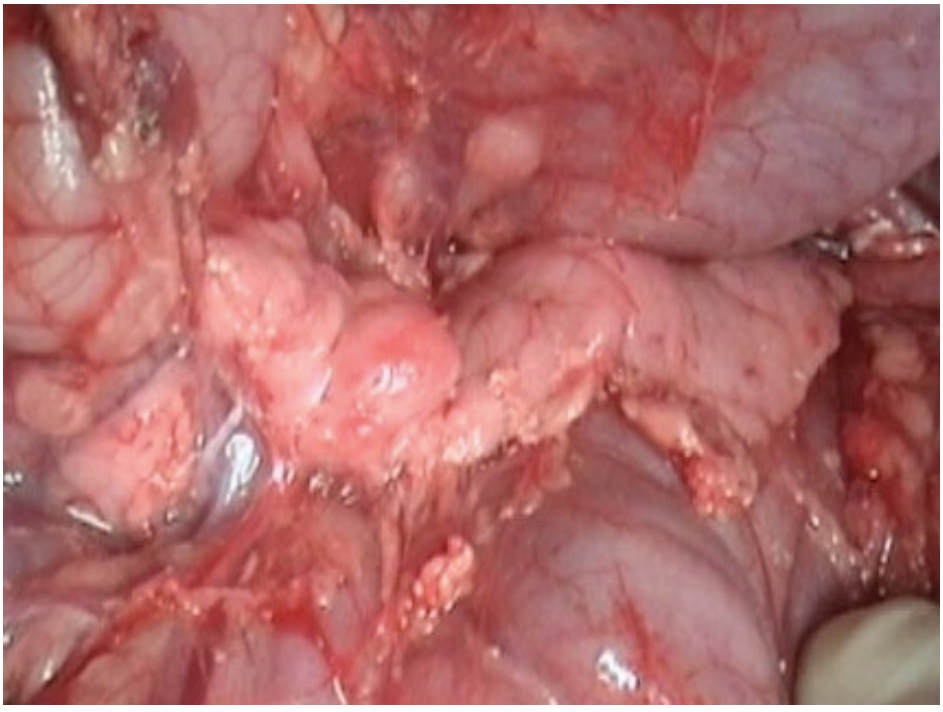

Fig. 1. Full exposure of the pancreas intra-operative view.

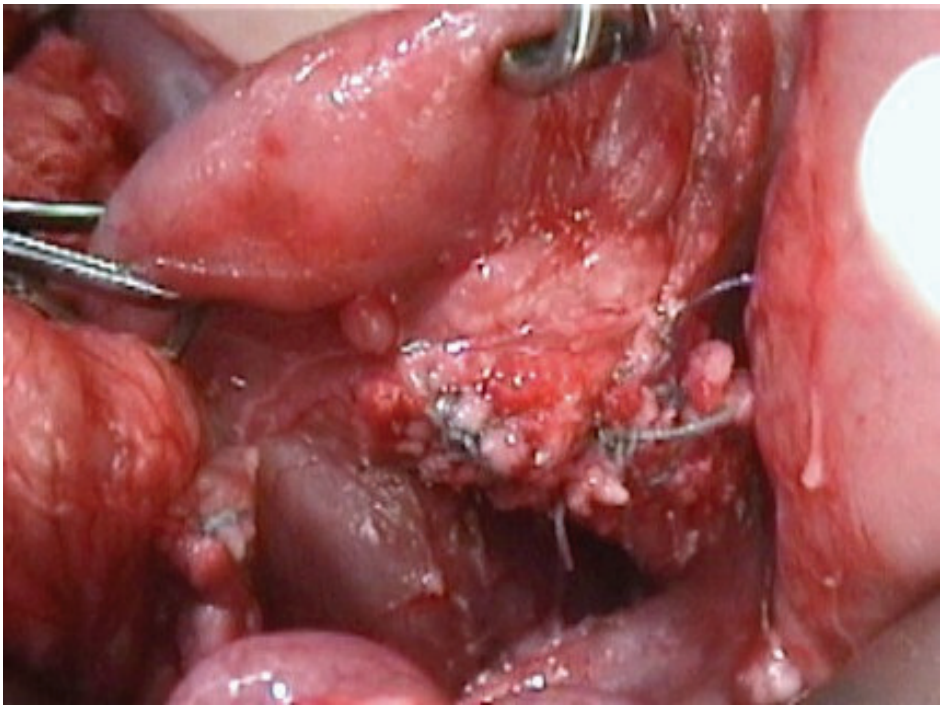

Fig. 2. Post near- total pancreatectomy.

boarder. This very much facilitates the dissection of the tail and body, thus reducing the operative time of the procedure. The dissection continues toward the uncinate process. The superior mesenteric vessels mobilized to the left and the uncinate process, and the head carefully dissected until the common bile duct identified above the first part of the duodenum. Then, resect the pancreas to the Lt of the intrapancreatic common bile duct leaving rim of the pancreatic tissue covering the duct and inner aspect of the C loop of the duodenum. No further trial of resection of pancreatic tissue as this will increase the risk of injury to the common bill duct. Gentle pressure applied on the liver and gall bladder to help in the identification of the common bile duct, and to exclude its injuries and bile leakage. The pancreatic duct was ligated. Intra-peritoneal drain was left in the pancreatic bed for 48-72 h postoperatively. Gastric tube was applied, broad spectrum antibiotic started and continued for 5 days. The resected pancreatic tissue sent for histopathological examinations. Intravenous nutrition continues until patient tolerates the oral intake within 3-5 days. Blood glucose monitored

frequently, both intra-operatively and post-operatively. Accordingly, administration of insulin was given to patients who developed hyperglycemia, but if the patient remained hypoglycemic (blood glucose ≤ 3.33 mmol/L), a second cycle of medical therapy (diazoxide and octreotide) was started. Glucose infusion was continued and adjusted according to the infant blood glucose. Patient clinical follow-up data was also reviewed.

Statistical Analysis

Data was gathered on a digital datasheet from KAUH Phoenix database and patient clinical charts from KAU archives. Tables were exported to the SPSS version 16 software, where the data was analyzed. Continues variables were presented as means and SD and categorical data as percentages. This study was approved by the Biomedical Ethics Department at Faculty of Medicine, KAU.

Results

In our cohort, 12/28 infants (43%) had ICDS. The remaining enrolled patients 16/28 (57%) had transient hypoglycemia of infancy. Of those with transient hypoglycemia, 4/16 had intrauterine growth retardation, 10/16 had a history of neonatal infection, 9/16 had a history of macrosomia, and one had a history of preterm delivery. In this group, only 3/16 patients (18.6%) had a history of consanguinity and only 1 patient had a mother with insulin dependent *diabetes mellitus* (IDDM). The majority of these patients 11/16 (68.8%) displayed signs of hypoglycemia in the first day of life, while the remaining infants developed hypoglycemia between 2-3 days of life. Mean and SD for the duration of recurrent episodes of hypoglycemia in these infants were 10±7.3 days, respectively (ranging between 4 to 30 days). Only 1 patient in this group suffered from seizures due to a history of hypoxic ischemic encephalopathy during his delivery. None of the remaining infants with transient hypoglycemia of infancy suffered any seizures or reoccurrence of their disease upon spontaneous recovery, and only two required diazoxide therapy. Mean, SD and median of follow-up for patients with transient hypoglycemia of infancy were 11.2, ± 6.6, and 12 months, respectively (ranging from 2 to 29 months). The main reason for

pediatric clinic follow-up in these patients were routine vaccinations in 8/16 (50%) patients.

Regarding infants with persistent hypoglycemia of infancy, ICDS, all were the result of a full-term pregnancy except 1 preterm infant. The birth weights ranged from 3 to 4.9 kg (mean and SD were 4.03 ± 0.67 kg, respectively). Consanguinity was prevalent in our cohort of ICDS infants (7/12, 58.3%), 6 parents were first-degree cousins and 1 were second-degree cousins. Two mothers were gestationally diabetic, 4 mothers had non-insulin dependent diabetes mellitus, and 1 mother had IDDM, the later 2 were treated with insulin during pregnancy. Four patients had history of fetal macrosomia (33.3%), and none had history of intrauterine growth retardation. Current patient ages ranged from 2 to 53 months (mean and SD were 27.9, ± 16.2 months, respectively). The age of the first documented hypoglycemia ranged from first day of life to 12 months. Seizures were the presenting symptom in 8/12 children (66.7%), 5/8 of these children with seizures were born outside our center and had a delayed referral, thus a delay in therapy initiation. Sweating, tremors and apnea were the presenting symptom in 4/12 patients (33.3%). All patients had inappropriately elevated serum insulin level and required high glucose infusion of more than 12 mg/kg/minute (range, 14-25 mg/kg/minute). Insulin levels during hypoglycemia ranged from 18.6 to 81.7 μm/ml (mean and SD, 32.2 ± 12.4 μm/ml, respectively). Insulin to glucose ratio ranged from 0.4 to 3.5 (mean, SD and median, 1.6, ± 0.9 and 1.5, respectively). All patients had negative urine ketones and normal growth hormone, cortisol and ACTH levels, which were collected during hypoglycemia. Ammonia level was measured for all ICDS subjects and was elevated in 10/12 (83.3%). Brain MRI and CT studies showed that 4/12 patients (33.3%) had brain atrophy; all of them were developmentally delayed, upon neurological assessment. Electroencephalogram was performed in 6/12 children with a history of hypoglycemic convulsion and delayed development. It showed mild diffuse slow electrical cortical discharge with no epiliptiform discharges in 2/6 patients.

All patients with ICDS were treated initially medically with intravenous glucose infusion and frequent feeding supplemented with complex carbohydrates (Polycose / corn starch). Only 5/12 patients (41.7%) had successful medical management, while the remaining 7 (58.3%) underwent near-total pancreatectomy due to failure of medical

treatment. Diazoxide dosage ranged from 10 to 20 mg/kg/day (mean, SD and median, 13.2, ± 3 and 13.5 mg/kg/day, respectively) in 3 divided doses per day, was used in 11 patients. The duration of diazoxide treatment ranged from 9 days to 26 months (mean, SD and median, 3, ± 7 and 1 month, respectively). Octreotide was used in 5/12 patients (41.7%) as an adjunctive therapy to diazoxide.

Near-total pancreatectomy was done *via* open laparotomy in all patients. The histopathology of all the resected pancreases confirms the diffuse nature of the disease. Postoperative complications included postoperative wound infection in 2/7 patients. No patients had bile leakage or injuries to the common bile duct. The spleens in all operated patient were preserved. No patients required repeat pancreatectomy. Only 1 patient died, due to persistent fungemia.

Mean, SD and median of follow up for ICDS patients were 14.8, ± 6, and 13 months, respectively (ranging from 3 to 30 months). All patients with ICDS were followed up to at least 1 year of age; expect one who did not attend clinic follow-ups after 3 months of hospital discharge. Five patients of ICDS developed IDDM and required regular insulin injections, 3 of which had undergone near-total pancreatectomy, two of them experienced weight gain. Four patients suffered from repeated hypoglycemic seizures during the follow-up period. Two (2) of them were pancreatectomized; all of them started second cycle of medical therapy.

Discussion

Hyperinsulinism is the single most important cause of persistent hypoglycemia in infants beyond the first few days after birth. Not all hypoglycemia of infancy is caused by ICDS, indeed some can be transient and might spontaneously resolve without the need for surgery or prolonged medical therapy. The differential diagnosis of hypoglycemia presenting in infancy varied, however, only a few diagnoses make up the bulk of cases. A convenient way to consider the differential is to divide it into transient or persistent/recurrent hypoglycemia. There are several causes of transient hypoglycemia of infancy, mainly maternal and neonatal conditions. Maternal conditions include intrapartum glucose given to the mother at a high rate, certain drug such as terbutaline and oral hypoglycemics, and diabetes in pregnancy. Neonatal conditions

include transient developmental immaturity of critical metabolic pathways, birth asphyxia, infection, hyperviscosity, and erythroblastosis fetalis[2,19]. In our cohort of patients with transient hypoglycemia of infancy, 3/16 mothers had gestational diabetes mellitus, 4/16 had fetal intrauterine growth retardation, 10/16 suffered from infection, and 1 had a history of hypoxic ischemic encephalopathy. There are several red flags that should merit pediatrician's attention as risk factors related to the development of hypoglycemia of infancy. These include: 1) Infants of diabetic mothers, 2) macrosomic newborn, 3) Intrauterine growth retardation, 4) Stressed infants (*i.e.*, difficult delivery, low Apgar < 7 at five minutes), 5) Infants of mothers on tocolytics (terbutaline, ritodrine), oral hypoglycemics or propranolol within 72 hrs before delivery, 6) Premature infants (< 37 weeks gestational age), 7) Postmature infants (> 42 weeks gestational age)[19-21]. Hypoglycemia of infancy has motleys presenting symptoms or could also be asymptomatic. The symptoms include: apnea, jitteriness, exaggerated moro reflex, irritability, poor sucking or feeding, cyanosis, hypotonia, lethargy or coma, temperature instability, seizure, tachypnea, heart rate abnormalities (slow or fast), abnormal cry or vomiting. Pediatricians should bear in mind that because these symptoms are fairly nonspecific, the differential should include other entities such as sepsis, hypocalcemia or intracranial hemorrhage, as appropriate for the clinical setting [21,22].

Islet cell dysmaturation syndrome (ICDS) is a rare inherited disorder with a predominant sporadic etiology. However, in Saudi Arabia and other regions where consanguinity is highly prevalent, the familial cases are common[4,8,9,23]. In our cohort of ICDS patients, consanguinity was present in 58.3%; other studies reported similar findings (60.5% and 58.1%). Also reported the hypoglycemic convulsions as the most common presenting complaint similar to our patients (66.7%)[8,9]. The mean insulin level was 32.2 μm/ml with a mean insulin to glucose ratio of 1.6, which is relatively lower than the levels reported in other studies[8,9,26]. Neonatal ICDS is a major risk factor of severe mental retardation, developmental delay, and epilepsy. These infants are especially vulnerable, as they do not produce ketone bodies during hypoglycemia. Menni *et al.*[25], retrospectively studied 90 patients with ICDS, and found that 21% had psychomotor retardation and 13% had epilepsy. In our cohort of ICDS patients, 66.7% of the patients had hypoglycemic convulsion and 33.3% were developmentally delayed. The

prevalence of developmental delay in our group related to late referral of the cases with severe attack of hypoglycemia, and unresponsiveness to medical therapy.

Medical therapy with diazoxide and octreotide has been successful in several studies[26,27]. Less than half of ICDS patients in our cohort showed a response to medical therapy alone (41.7%). Several studies reported that the extent of surgical resection in near-total pancreatectomy endangers future islet cell function and increases the incidence of IDDM, which is correlated with age[28,29]. Furthermore, near-total pancreatectomy does not only affect the endocrine function of the pancreas but also the exocrine function. In spite of none of our patient did show any clinical exocrine insufficiency, several studies reported subclinical exocrine pancreatic insufficiency in pancreatectomized ICDS children[30,31]. The majority of our ICDS patients were treated surgically (58.3%) and only 41.7% did not require surgery. Other studies reported even higher percentage of their patients require near-total pancreatectomy (79.1% and 76.3%)[8,9]. A total of 5 patients in our group developed IDDM, 3 of which were pancreatectomized; however, 2 were not. Development of IDDM in our non-pancreatectomized ICDS patients may suggest that those with ICDS will naturally develop diabetes, whether they were treated medically or surgically or even if they are left untreated. Seino *et al.*[32] reported a possible predisposing factor to hyperglycemia in ICDS children. Another possible contributing factor to the development of IDDM in these patients is the use of octreotide, which was reported to cause pancreatic β-cell apoptosis[33]. Islet cell dysmaturation syndrome (ICDS) carries a high risk of mortality and morbidity in survivors, which was estimated to be as high as 45%[24]. Only 1 patient died in our group due to persistent fungemia, other studies had higher mortality rates[8,9].

Conclusion

Islet cell dysmaturation syndrome (ICDS) is relatively common in Saudi Arabia, mainly due to the high prevalence of consanguinity but not as high as reported, this incidence should be re-evaluated. Early medical intervention is imperative in order to avoid permanent neurological complications. The morbidity in survivors of ICDS is high and calls for greater awareness, early diagnosis and genetic counseling as this can be a

familial disorder. Medical management alone can be successful in controlling ICDS; however, surgery is required in certain cases when medical treatment fails. It is believed that children with ICDS are prone to develop *diabetes mellitus* later in life, which is a process that can be accelerated by pancreatectomy.

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أنماط متلازمة لخلل نضوج خلايا جزر البنكرياس بين الرضع السعوديين

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جدة – المملكة العربية السعودية

المستخلص. متلازمة خلل نضوج خلايا جزر البنكرياس هي السبب الأكثر شيوعا لنقص السكر في الدم في مرحلة الطفولة. في هذه الدراسة نصف أنماط متلازمة خلل نضوج خلايا جزر البنكرياس بين الرضع الذين عانوا من نقص السكر في الدم. وقد أجريت هذه الدراسة على ٢٨ مريض بمرحلة الطفولة، كلهم يعانون مع نقص السكر في الدم، بين عام ٢٠٠٧ و ٢٠١١م ، متوسط أعمارهم كان ١٢,٨±٦,٨ أشهر. تم تشخيص خلل نضوج خلايا جزر البنكرياس على أساس ارتفاع الجلوكوز بالدم، وارتفاع نسبة الإنسولين / الجلوكوز، والكيتونات البولية سلبية، وإنخفاض حاد بالسكر بالدم لفترة تتجاوز الستة أشهر. خضع جميع المرضى المشاركين بهذة الدراسة إلى تقييم للجهاز العصبي سواء بالفحوصات الإشعاعية أو الرسم الكهربائي. ولقد تم استئصال شبه كامل للبنكرياس لدى المرضى الذين لم يستجيبوا للعلاجات الطبية الدوائية. جميع المرضى المشاركين بهذة الدراسة كانوا يعانون من نقص السكر في الدم مع عدم القدرة على الصيام. تم تشخيص نقص سكر الطفولة العابر في الدم في ٥٧٪ من الحالات المشاركة بهذة الدراسة العلمية وتم تشخيص متلازمة خلل نضوج خلايا جزر البنكرياس في ٤٣٪ من الحالات. ثمانية مرضى عانوا من التشنجات الدماغية نتيجة نقص السكر بالدم.

معظم الأطفال الرضع المشاركين (٥٨,٣٪) بهذه الدراسة خضعوا لاستئصال شبه كامل للبنكرياس. ثلاثة مرضى من الذين خضعوا لاستئصال شبه كامل للبنكرياس اصيبوا بمرض السكري المعتمد على الإنسولين. اثنان من المرضى الذين عولجوا بالوسائل الطبية الدوائية فقط أصيبوا بداء السكري المعتمد على الإنسولين وزيادة الوزن. ولقد تم متابعة غالبية المرضى المشاركين بهذه الدراسة (٩١,٧٪) إلى سن سنة واحدة من العمر على الأقل (متوسط المتابعة كان ١٤,٨±٦ أشهر). ولقد تعرض أربعة من المرضى المشاركين بهذة الدراسة للتشنجات المتكررة بسبب نقص سكر الدم خلال فترة المتابعة. التدخل الطبي المبكر ضروري لتجنب الضرر العصبي الناتج عن متلازمة خلل نضوج خلايا جزر البنكرياس في مرحلة الطفولة. مرضى متلازمة خلل نضوج خلايا جزر البنكرياس المعالجية بالوسائل الجراحية والطبية الدوائية هم جميعًا عرضة لخطر الأصابة بمرض السكري المعتمد على الإنسولين. الاعتلال بعيد المدى في الناجين من متلازمة خلل نضوج خلايا جزر البنكرياس عالية وتدعو إلى زيادة الوعي والتشخيص المبكر وتقديم المشورة الوراثية.