Subtotal Pancreatectomy for Congenital Hyperinsulinism: Our Experience and Review of Literature

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Abstract Congenital hyperinsulinism (HI) is characterized by profound hypoglycemia caused by inappropriate insulin secretion. HI is a heterogeneous disorder with at least two histologic lesions and several implicated genes. If HI is caused by a focal lesion, elective surgery is the treatment of choice because it leads to complete recovery without diabetes. On the contrary, near-total pancreatectomy though recommended for diffuse HI, long-term risks of endocrine and exocrine deficiencies are present. Between the years 2006–2011, three patients of HI were referred to and operated by a single surgeon. The preoperative diagnosis was confirmed by recurrent hypoglycemia, inappropriately high insulin levels, and augmented glucose requirements. The medical records of all three patients were reviewed to study their clinical features, medical and surgical treatment, and postoperative outcome (short- and long-term). There were three patients in this series (male/female ratio, 1:2), all presenting in the neonatal age. All patients failed medical treatment, and radiological imaging did not reveal any pancreatic lesion. All patients underwent subtotal (80 %) pancreatectomy. Two patients had diffuse type of HI and one focal HI. One patient had transient hyperglycemia for 3 months, which needed insulin supplementation. No patient has developed recurrent hypoglycemia, malabsorption syndrome, or any neurological sequelae until the last follow-up. Doing subtotal or near-total pancreatectomy in diffuse type of HI still remains controversial as one has a higher risk

of recurrent hypoglycemia, while the other has a higher rate of insulin dependent diabetes mellitus. Subtotal (80 %) pancreatectomy may be considered as the primary modality of surgical intervention in diffuse type of HI, especially when the diagnostic facilities are limited or diagnosis is not known after preliminary investigations. This minimizes the chances of postoperative diabetes mellitus, and redo surgery can always be considered if there is recurrent hypoglycemia.

Keywords Congenital hyperinsulinism · Hypoglycemia · Subtotal pancreatectomy · Nesidioblastosis

Introduction

Transient hypoglycemia is the most common metabolic abnormality in neonates and is seen in 4 per 1,000 term infants and 6 per 1,000 preterm infants [1]. Congenital hyperinsulinism (HI), first described by McQuarrie, is the most common cause of severe recurrent hypoglycemia in neonates and infants [2]. Laidlaw coined the term nesidioblastosis in 1938, based on his understanding of a diffuse ducto-endocrine B cell proliferative disorder of the pancreas [3]. Glaser proposed the term persistent hyperinsulinemic hypoglycemia in infancy (PHHI) in 1989, which incorporated the focal and diffuse pancreatic involvement associated with hyperinsulinism and hypoglycemia, which if not adequately treated, will result in severe brain damage and death [4]. At present, the denomination “congenital hyperinsulinism” is preferred over former names like “idiopathic hypoglycemia of infancy,” “nesidioblastosis,” and “PHHI” because HI is genetic not idiopathic; nesidioblastosis was found to be a normal feature of the pancreas in early infancy, and HI can persist from infancy to adulthood [5]. Conventional radiological imaging is often normal and unable to distinguish between the two forms [6]. Efforts should be made to differentiate between the

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focal and diffuse type since the surgical treatment differs. Focal lesions are cured by local resection, while diffuse lesions may require near-total pancreatectomy, putting the patient at risk for insulin-dependent diabetes in the future [1, 7]. We present our series of three patients with HI who had undergone subtotal (80 %) pancreatectomy. The postoperative outcome in all three cases is good with no long-term recurrence of hypoglycemia, endocrine deficiencies, malabsorption syndromes, and neurological sequelae.

Patients and Methods

Between the years 2006–2011, three patients of HI were referred to and operated by a single surgeon in a tertiary care municipal children's hospital. The preoperative diagnosis was confirmed by recurrent nonketotic hypoglycemia, inappropriately high insulin levels, and augmented glucose requirements. The medical records of all three patients were reviewed to study their clinical features, age of presentation, medical and surgical treatment, and postoperative outcome (short- and long-term). All patients are on regular follow-up with the shortest duration of follow-up being 1 year (period of follow-up: patient 1—3 years, patient 2—2½ years, patient 3—1 year).

Results

The clinical details of the patients are given in Table 1. There were three patients in this series whose age of onset of symptoms ranged from day 1 to day 22 of life, but none presented in the postneonatal age. The male/female ratio was 1:2. The average birth weight was 3.5 kg. Patient 1 presented initially with lethargy at birth and poor feeding followed by seizures; patient 3 had hypotonia and poor feeding initially followed by convulsions, while convulsions was the presenting feature in patient 2. All patients were started on medical management, but only patient 2 responded for a while and was discharged home thrice before decision was taken to surgically intervene in view of inadequate glycemic control. Patients 1 and 3 underwent surgery in their first admission itself. Insulin levels were elevated in all three patients, i.e., >10 mU/l in the presence of nonketotic (urine ketones—negative) hypoglycemia with glucose requirement >12 mg kg⁻¹ h⁻¹ in all three. All three patients had low serum-free fatty acid levels and an inappropriate hyperglycemic response was noted after glucagon infusion in patient 1. Radiological imaging in all cases revealed normal pancreatic morphology (abdominal USG-2, CT scan, MRI-1 each). All patients underwent 80 % subtotal pancreatectomy, mean age of surgery being 41 days. In surgery, all the pancreatic tissues distal to the right of the superior mesenteric vessels were resected (Fig. 1). Postoperative

Table 1 Clinical details of the cases of congenital hyperinsulinism

Case no.	Age of onset	Sex	Birth Wt. (kg)	Clinical features	Insulin levels (mU/l)	Medical treatment and duration	Response to medical treatment	Age at Sx (in days)	MAS/Sec. DM	Neuro development/recurrent hypoglycemia	Follow-up duration (years)	Histopathological type
1	Day 1	F	3.7	Seizures, lethargy, poor feeding	28	Dextrose, diazoxide, glucagon, nifedepine, octreotide for 9 days	Seizures controlled, hypoglycemia persistent	10	—/transient	N/—	6	Diffuse
2	Day 22	M	3.2	Seizures, apnea	11	Diazoxide, octreotide for 3 months	Initially, seizures, hypoglycemia controlled. later, recurrence	90	—/—	N/—	4	Diffuse
3	Day 3	F	3.6	Seizures, poor feeding, hypotonia	12	Diazoxide, octreotide for 3 weeks	Seizures controlled, hypoglycemia persistent	24	—/—	N/—	1	Focal

MAS malabsorption syndrome, Sec. DM secondary diabetes mellitus, N normal, Sx surgery, Wt weight

Fig. 1 Intraoperative picture showing dissection of the pancreas up to the right of the superior mesenteric vein

course was uneventful in all patients, and all of them have remained seizure-free until date. On histopathology, patient 1 and 2 had diffuse form of HI (diffuse hyperplasia of beta islet cells), while patient 3 had a focal lesion in the body of pancreas. Patient 1 had transient hyperglycemia (fasting blood glucose, 150–250 mg%; insulin levels, 2–3 mU/ml) for 3 months which needed insulin supplementation but gradually was weaned off insulin. All patients are normoglycemic (fasting blood glucose, 80–120 mg%; insulin levels <3 mU/ml; HbA1c <6 %), and no patient has developed recurrent hypoglycemia, malabsorption syndrome, or any neurological sequelae (epilepsy, delayed milestones) until the last follow-up.

Discussion

Congenital HI comprises a group of different genetic disorders with the common finding of recurrent episodes of hyperinsulinemic hypoglycemia due to an inappropriate secretion of insulin by the pancreatic β cells [5, 7]. In infants, the estimated annual incidence is 1 in 50,000 births for the sporadic form but may be as high as 1 in 2,500 births in societies with high rates of consanguinity, especially in the Arabian Peninsula [5, 8, 9]. The most common age for presentation is the neonate and infant. Presentation beyond the age of 2 years is rare [1]. All the patients in our series presented first in the neonatal age.

Majority of the children are macrosomic at birth and mild to moderate hepatomegaly may be present [1, 5, 7]. Hypoglycemic features may present within 3 days of life [1, 5]. The mean birth weight in our series was 3.5 kg, which is relatively large for an Indian population of low socioeconomic strata. Two of three patients presented within the first 3 days of life. Presenting features include lethargy, apnea, poor feeding, and hunger seizures. Tremors, cyanosis, hypotonia, and hypothermia may also be present [1, 5, 7–9]. Generalized tonic clonic seizures are seen in half of the cases [1, 10]. Seizures and poor feeding were the most common presenting features in our series.

In neonates, nonketotic hypoglycemia (glucose <36 mg/dl) glucose requirements of more than 6 to 8 mg kg⁻¹ min⁻¹ to maintain plasma glucose levels above 45 mg/dl, inappropriately high insulin (>3 mU/l), and c-peptide levels, together with inappropriately low free fatty acid and ketone body concentrations during hypoglycemia, glycemic response to glucagon, and absence of ketonuria establish the diagnosis of HI. The measurement of blood ammonia concentration is recommended nowadays, in view of the recent description of the syndrome of hyperammonemic hyperinsulinism [1, 9]. All our patients had nonketotic hypoglycemia (<36 mg/dl), high insulin levels (>3 mU/l), and high glucose requirement (>12 mg kg⁻¹ min⁻¹).

The histopathology of HI is heterogeneous and is hallmarked by the presence of ducto-endocrine proliferation, supernumerary small endocrine groups, and large endocrine areas [11]. Broadly, on histopathology, there are two forms of HI: the focal form (FoHI), which comprises about 30 % of cases, and the diffuse form (DiHI), which comprises about 70 % of cases. In our series, one patient (33 %) out of three had FoHI. The focal form, as the name signifies, is characterized by the presence of abnormal β cells in one or more focal areas inside the pancreatic tissue. The lesion measures about 2.5–7.5 mm in diameter. The diffuse form of the disease shows the presence of abnormal β cells in all sections of the pancreas. Atypical forms may be present in which the pattern of pancreatic involvement is of the diffuse type, but it is found only in one large area of the pancreas [5–7].

HI is caused by genetic defects in key genes regulating insulin secretion. The genetic basis of CHI involves mutations in eight key genes (ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A, and UCP2) identified so far, which regulate insulin secretion from the β cells. The most severe forms are due to recessive inactivating mutations in *ABCC8* and *KCNJ11*, which encode the two components of pancreatic β cell ATP-sensitive potassium channel [encoding for the two proteins sulfonylurea receptor 1 (*SUR1*) and inward-rectifying potassium channel pore-forming (*KIR6.2*) of the pancreatic β cell KATP channel, respectively] [5, 7, 9].

The primary concern in this illness is neurologic injury secondary to severe hypoglycemia leading to epilepsy, developmental delay, learning disability, cerebral palsy, or other forms of brain damage [5, 6, 12]. Medical management deals with maintenance of euglycemia and consists of dietetic measures, parenteral nutrition, diazoxide, glucagon, calcium channel blockers (nifedipine), and octreotide [1, 5, 8]. In recent times, cases treated with long-term administration (9 months to 5 years) of octreotide and glucagon (up to 4 years) have been reported, although long-term results are awaited [13, 14].

The indications for surgical intervention include poor compliance or failure of medical management and presence of focal lesion amenable to treatment [1, 5, 8, 15]. In our series, all patients were started on medical management with a

combination of drugs, but normoglycemia could not be maintained on drugs and diet alone, hence surgical intervention had to be considered. Seventy percent of neonatal-onset patients requires some form of pancreatic surgery since they did not respond to diazoxide and diet or to a carbohydrate-enriched diet alone as compared to only 28 % of the patients in infancy/childhood onset group [16]. All of our patients had a neonatal onset, and all eventually needed surgery due to failure of medical management.

Noninvasive imaging techniques (ultrasonography, computed tomography, magnetic resonance imaging) and celiac axis angiography have not been shown to be of value in the preoperative evaluation of HI [7, 9]. Even in our series, radiological imaging did not pick up any mass lesion in the pancreas. Efforts should be made to differentiate between the focal and diffuse type since the surgical treatment differs. Cretolle et al. recommended preoperative differentiation between the focal and diffuse form of the disease and localization of the focal lesions using percutaneous transhepatic pancreatic venous sampling [17]. Pancreatic venous sampling has been replaced now by [18-F]-L-DOPA positron emission tomography [PET] scans. The PET scan shows uniform uptake of [18-F]-L-DOPA throughout the pancreas in DiHI, while in FoHI, it is concentrated in various foci. The localization of focal forms can be improved by the fusion of the PET imaging with a CT angiography [1, 5, 6, 16]. Genetic analysis shows that the diagnosis of diffuse form is definitive when two mutations are found in *ABCC8* or *KCNJ11* genes or mutation(s) in the other genes involved in HI. In that case, PET scan is not necessary. A focal form is suspected only when one paternally inherited mutation is discovered in the *ABCC8* or *KCNJ11* gene. Thus, genetic analysis must be confronted with the PET imaging to categorize the form of HI, diffuse or focal [5, 18].

In focal lesions, partial pancreatectomy or local resection is recommended, and the prognosis is good when the resected specimen contains the lesion. The initial step in partial pancreatectomy or local resection for focal lesions must be multiple biopsies from the pancreas (head, body, and tail) with intraoperative diagnosis of hyperplasia on frozen section, as these focal areas are macroscopically invisible. This helps not only to differentiate a focal from a diffuse lesion but also the completion of the resection in a focal pathology [1, 5, 15, 18].

In cases with diffuse lesions, the optimal extent of resection of the pancreas is controversial. Pancreatic resection was first reported in 1934 by Graham and Hartman [19], and Gross in 1953 [20] performed 65 % resection of the pancreas. However, this procedure was plagued with recurrent hypoglycemia, requiring redo surgery or continuous medical therapy. Eventually, there was a gradual shift in opinion to subtotal pancreatectomy in 80–90 % resection which involved excision of distal pancreas distal to the right of the superior mesenteric vessels. This is associated with 25–50 % incidence of recurrent hypoglycemia [1, 5].

Recent literature suggests that infants with diffuse disease normally require a 95 % (near total) pancreatectomy. Near-total pancreatectomy incorporates removal of tail, body, uncinate process, and part of the pancreatic head. A rim of pancreatic tissue surrounding the common bile duct and along the duodenum is left behind. Near-total pancreatectomy is associated with a high incidence of diabetes mellitus and pancreatic exocrine insufficiency, hence reserved for those severe cases, where all medical therapy has failed [1, 5, 6, 15, 18].

In our study, we were not aware of the type of HI (focal or diffuse) prior to the surgery. But in view of intractable hypoglycemia threatening neurological damage, we performed subtotal pancreatectomy (80 %) in all our patients and sent the specimen for routine histopathological examination. Our approach was to offer subtotal resection and follow-up the histopathology and postoperative outcome instead of putting the child in risk of insulin-dependent diabetes mellitus and lifelong medication. We did this with the understanding and consent of the parents that the child may require subsequent surgery in the future, in case there is recurrence of hypoglycemia.

Major intellectual disability is more frequent in neonatal-onset patients and those who eventually required surgery [21, 22]. Insulin secretion seems more disturbed in pancreatectomized patients and insulin-dependent diabetes may develop during puberty [23]; however, it has been observed that patients who did not have surgery can still develop diabetes later in life [15]. Hence, an annual investigation of residual insulin secretion, based on pre- and postprandial plasma glucose and insulin levels at various intervals as well as measurement of glycated hemoglobin (HbA1c) and an oral glucose tolerance test, should be considered [5].

In our series, the postoperative outcome has been good irrespective of the histopathological report. All patients have attained normal milestones until date, with no neurological sequelae and no pancreatic exocrine or endocrine deficiencies. All the patients are on regular follow-up with periodical blood glucose and glycated hemoglobin levels.

In conclusion, conventional radiological imaging does not detect pancreatic lesions causing HI, and newer diagnostic modalities like 18-F-DOPA PET scan and intraoperative ultrasound with frozen section are required in the detection of focal lesions. Neonatal-onset HI invariably requires surgical intervention due to failure of medical therapy. Doing subtotal or near-total pancreatectomy in DiHI still remains controversial as one has a higher risk of recurrent hypoglycemia, while the other has a higher rate of insulin dependent diabetes mellitus.

In our limited experience with subtotal pancreatectomy for HI, we have had a very good outcome, with no incidence of recurrent hypoglycemia, endocrine deficiencies, and neurological development. Hence, we recommend subtotal (80 %) pancreatectomy as the primary modality of surgical

intervention in DiHI, especially when diagnostic facilities are limited or diagnosis is not known after preliminary investigations. This minimizes the chances of postoperative diabetes mellitus, and redo surgery can always be considered if there is recurrent hypoglycemia.

Conflict of Interest None

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