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HIPERINSULISMO CONGÉNITO

Delivering Safe and Effective Surgery in Congenital Hyperinsulinism

Cirugía segura y eficaz en hiperinsulinismo congénito

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Introduction

Congenital hyperinsulinism (CHI), through unregulated secretion of insulin from islet cells, is the most common cause of prolonged and persistent hypoglycaemia in neonates, and can result in irreversible brain damage if untreated. There are two distinct forms of the disease - focal and diffuse, depending on the pancreatic histopathology, with a small proportion having atypical features.

Although clinically identical, the focal and diffuse forms have histopathological and genetic differences. The focal disease is characterised by a tumour-like lesion with irregular edges surrounded by normal pancreatic tissue. There is focal adenomatous hyperplasia with endocrine enriched tissue structures, with few exocrine elements. These lesions are typically approximately 10 mm in diameter, but larger lesions have been observed. In the diffuse disease, there are large beta cells with abnormally large nuclei throughout the pancreas. Atypical lesions are associated with mosaic patterns of immature islet cells [(1)].

A significant number of patients with CHI are found to have underlying genetic causes, with the most frequent being mutations in the K-ATP channel genes, ABCC8 and KCNJ11. Paternal heterozygosity is commonly associated with the focal form of the disease. A mutation occurs in the other, active, copy of the gene during embryonic development. This second mutation only occurs in some cells in the pancreas. Maternal heterozygous, homozygous or compound heterozygous mutations in ABCC8/KCNJ11 are associated with diffuse CHI [(2)], with both copies present in all pancreatic cells. K-ATP channel genotyping enables stratification of treatment protocols of focal and diffuse CHI.

CHI occurs in 1:30,000 to 50,000 live births [(3)], with an incidence as high as 1 in 2,500 in areas of Saudi Arabia as a result of consanguinity. The rarity of this condition poses a number of challenges for the clinician, including recognition of the condition, diagnosis and providing effective evidence based on medical and surgical treatment.

Diagnosis

Hypoglycaemia in the neonate is a common phenomenon, and regardless of the cause, rapid recognition and treatment is necessary to prevent long-term neurological sequelae. A diagnosis of CHI is more likely when the hypoglycaemia is severe and prolonged, with dependence on significant glucose infusion requirements (GIR) exceeding 8 mg/kg/min [(4)]. Even with a clinical profile highly suggestive of CHI it is imperative to have biochemical confirmation with evidence of excess insulin action at the time of hypoglycaemia (≤ 3.0 mmol/L), namely detectable insulin or C-peptide, low or suppressed ketones (beta-hydroxybutyrate) and free fatty acids, and a glycaemic response to glucagon (>1.7 mmol/L).

Once a diagnosis of CHI is made, the patient should be discussed with and/or referred to a paediatric endocrinologist with expertise in managing this condition.

Imaging

PET/CT using ^{18}F-fluoro-L-DOPA is the gold standard imaging in patients with CHI, and provides anatomical and metabolic information that cannot be reliably achieved by other imaging methods. Imaging in CHI is dictated by the genetic results. In patients with no identified genetic mutation, imaging is used to ascertain whether the disease has appeared in its focal or diffuse form. There is a stark difference in the appearance of the pancreas in the two forms of CHI in PET/CT (Figure 1). In cases with a mutation suggesting of the focal form of the disease, the imaging identifies the location of the focus within the pancreas, demonstrating increased standardised uptake value (SUV) in the affected tissue (Figure 1), and is essential in surgical planning.

Medical management

After confirmation of the diagnosis of CHI, oral diazoxide should be commenced at 3-5 mg/kg/ day in three divided doses. This reduces insulin secretion from the β-cell by maintaining the K-ATP channel in the open state. It's effects are usually seen within 24-48 hours, with most patients experiencing a beneficial effect responding at low doses. Where there is little or no response, the dose may be increased by 2.5mg/kg/day every two days to a maximum dose of 15mg/kg/day. However, if the required dose is greater than 10mg/kg/day then the patient is probably diazoxide unresponsive, and second line treatment is therefore required, i.e., octreotide, which is a short-acting somatostatin analogue that reduces insulin secretion through a cAMP-mediated action. This should commence at a low dose (5 mcg/kg/day) in 4-6 divided doses (subcutaneous or intravenous injections), and may be increased to a maximum of 30 mcg/kg/day depending on the response. In severely affected patients, other treatment options include long-acting somatostatin analogues and sirolimus, but these are used off-label, and must be managed by a clinician with an expertise in managing CHI.

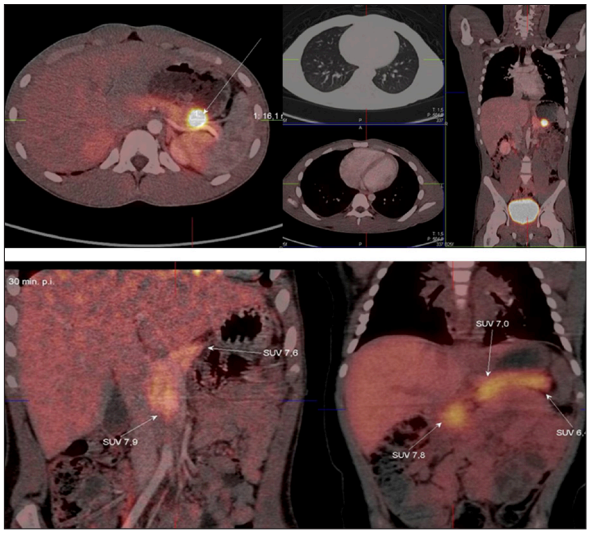

Figure 1. ^{18}F-fluoro-L-DOPA PET/CT in focal CHI (top image) and diffuse CHI (bottom image).

CHI may gradually resolve itself in some patients, and particularly in those without genetic mutations. In thsese cases, the medication should be gradually reduced then stopped as blood glucose levels permit.

Surgery

The first surgical procedure for CHI was performed in 1934 by Evarts Graham, who undertook pancreatic exploration for a possible adenoma. As the adenoma was not found, a subtotal pancreatectomy was undertaken with curative results [5]. Surgery should be performed in a specialist CHI centre, and is now tailored to the patient's needs. There are three different indications:

- curative lesionectomy in focal disease;
- subtotal pancreatectomy in diffuse disease resistant to medical therapy;
- biopsy when the diagnosis is uncertain due to conflicting results [6].

Regardless of the indication, surgery can be approached by an open technique or minimally invasive surgery (MIS). Open surgery is performed through an upper transverse incision with entry into the lesser sac to expose the pancreas. This approach enables easy identification of the common bile duct during subtotal pancreatectomy, and direct palpation of the pancreas which may be beneficial in identifying focal disease in the absence of a visual nodule. Four working ports are required if the MIS approach is adopted; a camera port, two working ports placed in the iliac fossae to increase the distance from the pancreas to the fulcrum and thereby improve ergonomics, and a port to allow instrument retraction of the stomach to ensure the maximum view of the pancreas. The latter can be replaced by a Nathanson retractor. A single incision laparoscopic approach has also been described [7].

Surgery for Focal Disease

Surgery in the focal form of CHI is curative, and is offered to all patients with this form of the disease. The use of ^{18}F-fluoro-L-DOPA PET/CT permits accurate preoperative identification of the location of the focus, permitting directed lesionectomy with preservation of the normal pancreatic tissue. Intraoperatively, after

the part of the pancreas that contains the focus is exposed it should be inspected for a macroscopically obvious focal lesion. There are various possible macroscopic appearances, ranging from an obvious dark pink lesion to subtle differences in the surface of the pancreas (Figure 2). Direct digital palpation may assist in locating a focus that cannot be identified visually, as many of these lesions are firmer than the surrounding normal pancreatic tissue.

After identification, the focus should be removed with a margin of normal pancreas to ensure complete clearance. A focal lesionectomy may be performed when the lesion is located in the tail or on the edge or surface of the pancreas, ensuring that there is no risk of damage to either the pancreatic duct or bile duct. Partial pancreatectomy is indicated when the lesion is in the body or tail of the pancreas and beside the pancreatic duct, as focal lesionectomy risks damage or division of the duct, resulting in pancreatic leak and/or pancreatitis.

For lesions in the head, simple resection is indicated when the focus is small and superficial. Lesions deep in the head pose a significant surgical challenge due to the risk of damage to the pancreatic and bile ducts. Roux-en-Y pancreaticojejunostomy and Whipples procedures have been reported [8]. This is a major undertaking, with long-term potential problems including biliary stricture or cholangitis, pancreatitis and peptic ulcer disease [9]. In these situations, the long-term risks of these major procedures need to be balanced with conservative treatment of medically managed patients whose symptoms may be resolved over time. Indeed, in our experience, we have had patients with focal disease in the head of the pancreas where laparotomy revealed no focus despite biopsies of the area indicated by imaging. Rather than performing resection of the head of the pancreas, we decided to abandon further surgical exploration and continue medical treatment. These patients required ongoing medical treatment for approximately 18 months, and are now euglycaemic.

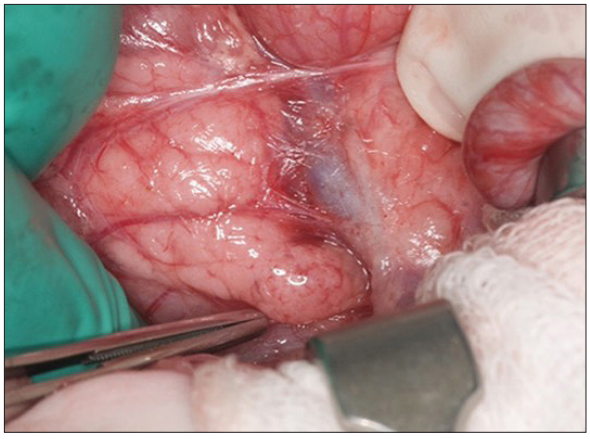

Figure 2. Focal lesion at end of forceps.

In all procedures for focal disease, the resected tissue should be sent for histological examination of the intraoperative frozen section to confirm that the resected specimen contains the focus. Resection of the focus may also lead to a rise in blood or subcutaneous glucose levels, requiring a reduction in the GIR. This takes place immediately during the procedure In some patients. However, as a number of patients have a high intraoperative GIR even following resection, intraoperative blood sugar levels cannot be relied on to confirm lesionectomy. Surgeons must trust the preoperative imaging and intraoperative frozen section when identifying and confirming resection of the focus, rather than trusting visual appearances and GIR as standalone markers.

Following successful removal of the focus, the cut surface of the pancreas should be covered in a fibrin sealant to reduce the risk of pancreatic leak. Drain insertion may be considered. We do not routinely insert drains for limited focal lesonectomies with a small area of cut pancreatic tissue. Postoperative management should adhere to enhanced recovery principles, with feeds introduced as soon as possible.

Surgery For Diffuse Disease

Advances in medical management have resulted in improved blood glucose control, reducing the requirement for surgery in patients with diffuse disease and thus avoiding long-term complications, including diabetes mellitus and exocrine insufficiency. Pancreatectomy is indicated when patients have a significant GIR which is near the total (95%) despite maximal medical therapy. This involves resection of the majority of the pancreas, leaving a small amount of tissue between the common bile duct (CBD) and the wall of the duodenum.

During surgery, the procedure commences with the tip of the tail being sent for intra-operative frozen section histological analysis to confirm the diagnosis of diffuse CHI. This is standard procedure in our institution, as the sequelae of this procedure is such that definitive diagnosis is essential before proceeding further. This is particularly important in diffuse CHI with no identifiable genetic mutation. Once the diagnosis is confirmed, the pancreas is dissected off the surrounding structures, starting at the pancreatic tail. During skeletonisation of the splenic artery and vein, great care must be taken to ensure that the arterial branches and venous tributaries are adequately sealed using diathermy. Dissection is continued by mobilising the neck and uncinate process of the proximal portal vein and superior mesenteric vein respectively. At this point it is essential to identify the CBD, which is then skeletonised as this structure indicates the limit of dissection. After the pancreatic tissue has been excised, the pancreatic bed must be inspected for haemostasis and for any evidence of lymphatic leak. The gallbladder must be

expressed, and the CBD examined for any evidence of bile leak indicating CBD damage. Fibrin sealant is sprayed to cover the pancreatic bed, and a drain is always inserted.

Post-operative management of these children is much more complex than for those undergoing surgery for focal CHI, and all these patients are managed in the paediatric intensive care unit. Blood sugar levels are more labile in the post-operative period, and require constant monitoring and management by a paediatric endocrinologist. Post-operative ileus is more common in this patient cohort, and feeding should be introduced gradually, as tolerated by the patient. This needs to be managed in coordination with the endocrinologist to ensure there is no impact on blood sugar control. The drain should remain *in situ* until the patient is fully fed, to ensure there is no lymphatic leak.

Surgery in Atypical Disease

This form of the disease poses challenges for the surgeon as a result of the multifocal and separate nature of the lesions. When surgery is indicated, the affected areas should be removed whilst preserving as much normal pancreatic tissue as possible, although extensive surgery may be required to ensure complete resection.

Gastrostomy insertion

Feeding problems (FPs) are common in seriously unwell children, and are frequent and complex in children with CHI. This was confirmed by a study at our institution, in which a third of children with CHI had significant FPs. FPs are associated with severe hypoglycemia at diagnosis requiring frequent glucagon infusion to normalize glucose levels, and patients with diffuse CHI undergoing subtotal pancreatectomy. In our experience, a number of focal CHI patients also had FPs [10]. Despite successful surgical interventions in these patients, FPs persist and gastrostomy insertion at the time of pancreatic surgery is therefore indicated. The gastrostomy tube can be removed when full oral feeding is established.

Improving outcomes in congenital hyperinsulinism

Rare diseases such as CHI pose a significant challenge to clinicians due to the lack of knowledge of the disease and inexperience in treating the disease, with occasional practice resulting in poor outcomes for patients. To address this issue, the United Kingdom Government and the National Health Service commission specialist services which are centralised in a small number of centres in order to improve care and support for patients with rare diseases.

Congenital hyperinsulinism in the UK is treated by two services, the Northern Congenital Hyperinsulinism (NORCHI) Service based at the Royal Manchester Children's Hospital, with some medical services at Alder Hey Children's Hospital, Liverpool, and at Great Ormond Street Hospital in London. An estimated 95 patients with CHI are born in the UK every year [11], and this centralised approach ensures that the clinicians involved in managing these children gain experience in all aspects of care.

As well as improving outcomes for patients, centralisation enables the identification of associated problems which would otherwise have not been observed if occasional practice was undertaken. The NORCHI service has noted these issues, including persistent feeding problems in children with CHI [10] and issues with catheter-related thrombosis in this patient cohort [12].

Management of these patients requires a multidisciplinary team which includes endocrinologists, specialist nurses and dieticians, as well as designated surgeons supported by anaesthetists with experience in the intraoperative management of CHI, and pathologists trained in histology for CHI. This approach is known to improve outcomes for patients undergoing surgery for the condition [13].

Improving surgical outcomes

It has been well documented that improved surgical outcomes are directly dependent on the number of procedures for a specific condition carried out in a given hospital and by a specific surgeon [14]. The NORCHI service has one lead pancreatic surgeon (RC) with over fifteen years of experience in pancreatic surgery, and a second surgeon (PF) with six years of experience. Both the surgeons operate together in all CHI cases, ensuring the maximum experience is attained. Seventy-four patients (24 diffuse, 43 focal, 3 atypical & 4 insulinoma) underwent 77 procedures (50 open, 16 laparoscopic & 11 laparoscopic converted from laparoscopic to open) at the Royal Manchester Children's Hospital between 2007 and 2024 (Figure 3). Three of the procedures were redo surgery for ongoing severe symptoms, and of the 11 cases converted

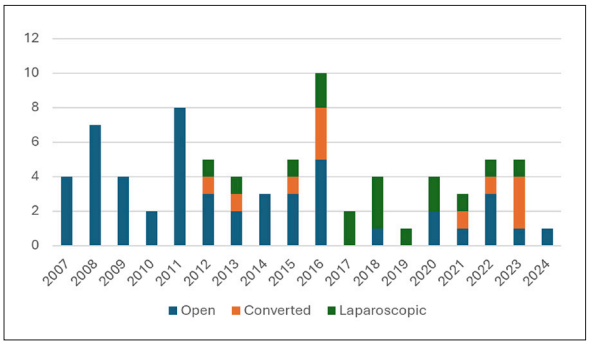

Figure 3. Number of cases of pancreatic surgery per year and surgical approach performed by the NORCHI Service, Royal Manchester Children's Hospital.

from laparoscopic to open, seven were for technical issues, three was diffuse on biopsy, and one was due to PET scan issues.

Of the patients that underwent surgery for focal disease, 89% were completely cured. The patients with ongoing symptoms included those for whom the focus could not be identified intraoperatively, and one patient's symptoms returned some months post-surgery, for reasons which are unclear.

Those treated surgically for diffuse disease have variable outcomes. 54% have ongoing symptoms which have required redo surgery in three patients, 33% are cured, and the remaining patients have diabetes mellitus. One of the latter also has exocrine insufficiency. Two of the atypical patients are cured, while all the patients treated for insulinoma are cured. Our outcomes are comparable to those of other large centres [8].

Pancreatic surgery in the adult population is known to be associated with high rates of wound infection, of 30-35%[15]. Reliable data in the paediatric population is not available, but our wound infection rate of 15.5% compares favourably to adult studies. There were two CBD injuries (2.6%) in our series. One of those was noted intraoperatively, and was repaired with no further problems. The second patient developed the leak a number of days after surgery, and this was successfully treated conservatively with no further surgery required. Other studies show that injury to the common bile duct occurs in up to 16% of patients [16].Skeletonisation of the splenic vessels during surgery can result in splenic injury, but no patient in our series experienced this complication. This is similar to other large centres [17] but less than the level of 2% published by other groups [16].

It is impossible to compare outcomes from large centres with centres that undertake occasional surgery due to a lack of data from these centres. However, hospitals that infrequently manage this condition have sought advice from NORCHI when multiple procedures have failed to achieve the therapeutic goal, demonstrating that inexperience leads to poorer outcomes.

Conclusions

Our experience demonstrates that the safest and most effective way to deliver surgery for congenital hyperinsulinism is to maximise the surgeon's exposure by centralising the management of this rare disease with support from a multidisciplinary team consisting of paediatric endocrinologists, nuclear medicine physicians and dieticians. This approach leads to positive outcomes and fewer complications.

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