Journal of the Endocrine Society, 2022, **6**, 1–7
https://doi.org/10.1210/jendso/bvac033
Advance access publication 15 March 2022
Clinical Research Article

Variation in Glycemic Outcomes in Focal Forms of Congenital Hyperinsulinism—The UK Perspective

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Abstract

Context: In focal congenital hyperinsulinism (CHI), localized clonal expansion of pancreatic β-cells causes excess insulin secretion and severe hypoglycemia. Surgery is curative, but not all lesions are amenable to surgery.

Objective: We describe surgical and nonsurgical outcomes of focal CHI in a national cohort.

Methods: Patients with focal CHI were retrospectively reviewed at 2 specialist centers, 2003-2018.

Results: Of 59 patients with focal CHI, 57 had heterozygous mutations in *ABCC8/KCNJ11* (51 paternally inherited, 6 de novo). Fluorine-18 L-3,4 dihydroxyphenylalanine positron emission tomography computed tomography scan identified focal lesions in 51 patients. In 5 patients, imaging was inconclusive; the diagnosis was established by frozen section histopathology in 3 patients, a lesion was not identified in 1 patient, and 1 declined surgery. Most patients (n = 56) were unresponsive to diazoxide, of whom 33 were unresponsive or partially responsive to somatostatin receptor analog (SSRA) therapy. Fifty-five patients underwent surgery: 40 had immediate resolution of CHI, 10 had persistent hypoglycemia and a focus was not identified on biopsy in 5. In the 10 patients with persistent hypoglycemia, 7 underwent further surgery with resolution in 4 and ongoing hypoglycemia requiring SSRA in 3. Nine (15% of cohort) patients (1 complex surgical access; 4 biopsy negative; 4 declined surgery) were managed conservatively; medication was discontinued in 8 children at a median (range) age 2.4 (1.5-7.7) years and 1 remains on SSRA at 16 years with improved fasting tolerance and reduction in SSRA dose.

Conclusion: Despite a unifying genetic basis of disease, we report inherent heterogeneity in focal CHI patients impacting outcomes of both surgical and medical management.

Key Words: focal lesion, hyperinsulinemic hypoglycemia, *ABCC8* gene

Abbreviations: ^{18}F-DOPA PET/CT, fluorine-18 L-3,4 dihydroxyphenylalanine positron emission tomography computed tomography; KATP, adenosine triphosphate-sensitive potassium; CHI, congenital hyperinsulinism; PI, pancreatic insufficiency; SSRA, somatostatin receptor analog.

Congenital hyperinsulinism (CHI) is characterized by recurrent hypoglycemia due to inappropriate, excessive insulin secretion from pancreatic β-cells and represents the most common cause of hypoglycemia in neonates [1]. The incidence of CHI in the UK is approximately 1 in 28 000, similar to other outbred populations, with greater incidence in consanguineous populations or those influenced by founder effects [2, 3]. Early recognition and appropriate management of CHI can prevent hypoglycemic brain injury and subsequent neurodevelopmental problems [4-6].

There are 2 main histopathological types of CHI, focal and diffuse, which have similar presentations but differ in the underlying genetic mechanism, histopathology, and management [7]. Mutations in at least 11 different genes (*ABCC8*,

Received: 27 November 2019. **Editorial Decision:** 25 February 2022. **Corrected and Typeset:** 13 May 2022

KCNJ11, *GLUD1*, *GCK*, *HADH*, *SLC16A1*, *HNF4A*, *HNF1A*, *PGM1*, *PMM2*, and *CACNA1D*) have been reported in up to 40% of CHI patients [1, 8-11] with the underlying genetic etiology unknown in the majority of cases. Focal CHI arises from a precise genetic mechanism whereby a paternally inherited *ABCC8* or *KCNJ11* mutation, combined with somatic loss of the maternal allele in the 11p15 region, results in overexpression of the paternally inherited allele [12-14]. This leads to imbalance between the maternally expressed cell cycle inhibition genes *H19* and *CDKN1C*, and the paternally expressed growth factor insulin-like growth factor 2, resulting in unhindered clonal expansion of endocrine-rich pancreatic cells and β-cell proliferation [15, 16]. In those with paternally inherited *ABCC8/KCNJ11* mutations, fluorine-18 L-3,4 dihydroxyphenylalanine positron emission tomography computed tomography (^{18}F-DOPA PET/CT) scan can be used to detect the anatomical location of the focal lesion [17, 18], with sensitivity ranging from 88% to 94% and specificity from 90% to 95% respectively [17, 19, 20]. Focal lesions are characterized by nodular hyperplasia of islet-like endocrine cell clusters with normal surrounding exocrine and endocrine pancreatic tissue [12]. This contrasts with the diffuse form, in which hyperfunctioning islets occur throughout the entire pancreas and nucleomegaly occurs in over 45% of cells within the islets [21].

Focal CHI is typically medically unresponsive [22, 23]. Surgical excision of the lesion is therefore the treatment of choice and curative in the majority of patients [24, 25]. However, focal lesions are heterogeneous in structure [26] and can be surgically challenging, for instance when located in the pancreatic head near important structures including the common bile duct and pancreatic duct. In such cases conservative treatment may be preferable to radical Whipple surgical procedures. Effective treatment with lanreotide has been reported in CHI patients with inoperable focal lesions [27, 28], but large cohort studies have not been undertaken to determine the contribution of nonsurgical conservative therapy to the management of focal CHI. In the present study, we have analyzed outcomes in children with focal CHI over the last 15 years in a national cohort from 2 UK specialist centers.

Materials and Methods

All cases of focal CHI diagnosed at 2 CHI specialist centers from January 2003 to May 2018 were retrospectively reviewed. CHI was diagnosed according to well-established criteria [29]. Referrals to the CHI center at Great Ormond Street Hospital (London), and the combined center at the Royal Manchester Children's Hospital (Manchester) and Alder Hey Children's Hospital (Liverpool) were received from neonatal units and tertiary pediatric endocrine centers from across the UK. The annual incidence of CHI averaged 150 over the period of the study.

The following patient data were obtained from case note review: baseline demographics (age, gender, gestational age, birth weight); diagnosis of focal CHI (age at presentation, genetic mutation status, ^{18}F-DOPA PET/CT scan result); initial management of hypoglycemia; details of pancreatic surgery (age at surgery, extent of resection, complications), long-term glycemic control (hypoglycemia resolution, ongoing need for hypoglycemia treatment, development of diabetes mellitus, and/or pancreatic exocrine insufficiency), and neurodevelopmental outcomes. Neurodevelopment was assessed by a combination of methods, including review by clinical psychologist, formal developmental assessment, and developmental pediatrician review. Neurodevelopmental assessment was not standardized owing to procedural differences at the 2 centers and diversity among the age groups. A patient was deemed responsive to medical therapy if intravenous support for hypoglycemia and glucagon could be discontinued, and euglycemia maintained on an age-appropriate enteral feeding regime and age-appropriate fasting tolerance.

Focal CHI was presumed in patients with CHI with a paternal heterozygous *ABCC8/KCNJ11* mutation and ^{18}F-DOPA PET/CT scan showing retention of ^{18}F-DOPA at 40 to 60 minutes postinjection relative to surrounding nonlesion pancreas and confirmed by standardized uptake values >1.5. In those patients undergoing surgery, focal CHI was confirmed on histopathology. ^{18}F-DOPA PET/CT scan was performed according to previously reported protocols adapted to local conditions at the 2 centers [30].

In patients undergoing surgery, surgery type was classified by extent. Lesionectomy was defined as resection of the focal lesion with or without an adjacent rim of normal pancreatic tissue. Subtotal pancreatectomy was defined as involving most of the pancreas, sparing a rim of pancreatic tissue adjacent to the duodenal curve. Extended focal surgery was reserved for intermediate cases with resection more extensive than lesionectomy but less than subtotal pancreatectomy.

All patients underwent a safety fast test prior to discharge regardless of medical or surgical management, with a requirement of bedside plasma glucose >3.5 mmol/L (63 mg/dL) for the duration of the fast. Fasting duration was variably 6 to 10 hours in infants (≤12 months of age) and 10 to 16 hours in older children. Medication was reintroduced postoperatively if a patient failed the safety fast or had recurrent hypoglycemic episodes characterized by plasma glucose <3.5 mmol/L. Medications included somatostatin receptor analogs (SSRAs) in all patients with postoperative hypoglycemia and sirolimus therapy in occasional patients unresponsive to SSRA therapy.

The study was been approved by the research ethics boards at both centers.

Results

Baseline Characteristics of Hyperinsulinism in Focal CHI Patients

Fifty-nine patients with focal CHI were identified over a 15-year period. Forty-five (76%) were male and presented at a median age of 1 day (range 1-240) with hypoglycemia (Table 1). Mutations in the adenosine triphosphate–sensitive potassium (K_{ATP}) channel genes were identified in 57 (97%) patients (Table 1 [31]), 49 in *ABCC8*, and 8 in *KCNJ11*. Fifty-one mutations were paternally inherited, while testing of parental samples in 6 cases did not detect the mutation, in keeping with the mutations having arisen de novo. In 1 patient, no mutation was identified either in peripheral blood lymphocyte or buccal mucosal DNA. In this child, a mosaic *ABCC8* mutation was identified within the resected pancreatic focal lesion with concomitant loss of the maternal allele at the 11p15 locus (Table 1 [32]). In 1 further patient, no mutations were identified in peripheral blood lymphocytes, but pancreatic DNA was not obtained to investigate for mutations within the lesion.

^{18}F-DOPA PET/CT scanning was performed in 56 patients; focal lesions were identified by localized isotope retention in 51 (91%) patients (Fig. 1). Three patients did not undergo scan due to unavailability of scanning facilities. Focal lesions were present evenly throughout the pancreas with similar frequencies in the pancreatic head (16, 31%), body and neck (15, 30%), and tail (17, 33%) (Fig. 1B). In 5 (9%) patients, ^{18}F-DOPA PET/CT scan did not demonstrate a clearly identified focus (Fig. 1A). Of these patients, 3 had a focal lesion that was identified by frozen section histopathology at pancreatic surgery and removed by lesionectomy (Table 1, patients 17, 19, 35 [31]). In patient 55, a focal lesion was not identified on intraoperative frozen section biopsy; no further pancreatic resection was performed, and the patient was medically managed long term. The family of patient 50, in whom a focus was not identified, declined surgical exploration; subsequent clinical management was medical.

All patients were initially prescribed diazoxide: 3 showed evidence of partial responsiveness to high-dose (15-20 mg/kg/day) therapy with maintenance of home-monitored plasma glucose >3.5 mmol/L and an increase in fasting tolerance (Tables 1-3). In the remaining 56 patients, diazoxide was ineffective: 7 of these patients directly underwent surgery without further trial of medication, while SSRA therapy with octreotide was used as second-line medication in 52 patients. Nineteen (36%) were responsive at a median (range) dose of 15.5 (7.5-40) µg/kg/day and 29 (56%) were deemed partially responsive to SSRA based on improvement in glycemic control with partial reduction in intravenous dextrose and/or glucagon infusion support. Four patients did not respond to octreotide.

Patients were categorized by the type of definitive management (Table 1 and Fig. 2): those who had resolution of CHI after surgery ("Surgery"); those who had hypoglycemia after surgery managed with medication ("Surgery + Medication"); and those managed with medication alone and did not undergo surgical resection of their focal lesion ("Medication").

Surgically Managed Patients With Focal CHI

Fifty-five patients (93%) were brought to pancreatic surgery (Fig. 2) at a median age of 4.0 months (range 1.1-36), of whom 30 underwent focal lesionectomy, 14 extended focal surgery, and 6 subtotal pancreatectomies. Five patients underwent biopsy only; in 4 patients, a focal lesion could not be located on frozen section histopathology while in the fifth patient, surgical localization of the lesion in the pancreatic head was challenging (Fig. 2). A focal lesion was inferred from the finding of normal pancreatic histology, excluding diffuse CHI, in the context of a lesion on ^{18}F-DOPA PET/CT scan and presence of a single K_{ATP} mutation (paternal in 4 patients, de novo in the fifth patient). After biopsy, no further resection was performed and these patients were managed with long-term medication (Fig. 2).

CHI resolved in 40 patients following pancreatic surgery (28 focal lesionectomy; 9 extended focal surgery; 3 subtotal) (Fig. 2). Subtotal pancreatectomy was converted from focal lesionectomy in 1 patient as the lesion was poorly demarcated, requiring wider tissue dissection (Table 1, patient 40 [31]). In the other 2 patients, lesionectomy resulted in loss of vascular supply to the pancreatic body and tail, necessitating wider resection. In 10 patients, hypoglycemia recurred after

Table 1. Baseline characteristics of patients with focal CHI

	All	Surgery	Surgery + medication	Medication
Number	59	44	6	9
n (%)	45 (76)	35 (80)	4 (67)	6 (67)
Median age at presentation, days (range)	1 (1-240)	1 (1-180)	1 (1-60)	5 (1-240)
Genetics, n				
Paternal K_{ATP}	51	39	5	7
ABCC8/KCNJ11	45/6	36/3	3/2	6/1
De novo K_{ATP}	6	3	1	2
ABCC8/KCNJ11	4/2	2/1	1/-	1/1
Negative	1	1	-	-
Other	1	1	-	-
^{18}F-DOPA PET/CT scan				
Number scanned	56	42	5	9
Focal lesion identified, n	51	39	5	7
Initial management				
Diazoxide responsive (partial)/total tried	3/59	1/44	1/6	1/9
Diazoxide median dose, mg/kg/day (range)	15 (5-21)	15 (5-21)	15 (15-20)	16 (10-20)
Octreotide responsive/total tried	19/52	13/37	0/6	6/9
Octreotide median dose, µg/kg/day (range)	20 (7.5-45)	20 (7.5-45)	20 (10-30)	17 (12-40)

Characteristics are shown for the entire cohort and by type of definitive management: (1) "Surgery," resolution of CHI after surgery including 4 patients who underwent a second surgery; (2) "Surgery + Medication," requiring medication for postoperative hypoglycemia including 3 patients who underwent a second surgery; (3) "Medication," those managed with medication alone including 5 patients taken to surgery in whom the focal lesion could not be found (Fig. 1). Mutations in the K_{ATP} channel genes *ABCC8* or *KCNJ11* were classed as paternal or de novo. The latter was presumed if a mutation was not detected in either parent. One patient ("Other") had maternal loss of heterozygosity and a monoallelic *ABCC8* mutation detected within the resected focal lesion but not in peripheral lymphocyte or buccal DNA [31]. For initial management, a patient was deemed responsive if intravenous fluids and glucagon could be stopped, and euglycemia maintained on enteral feeds at an age-appropriate frequency.

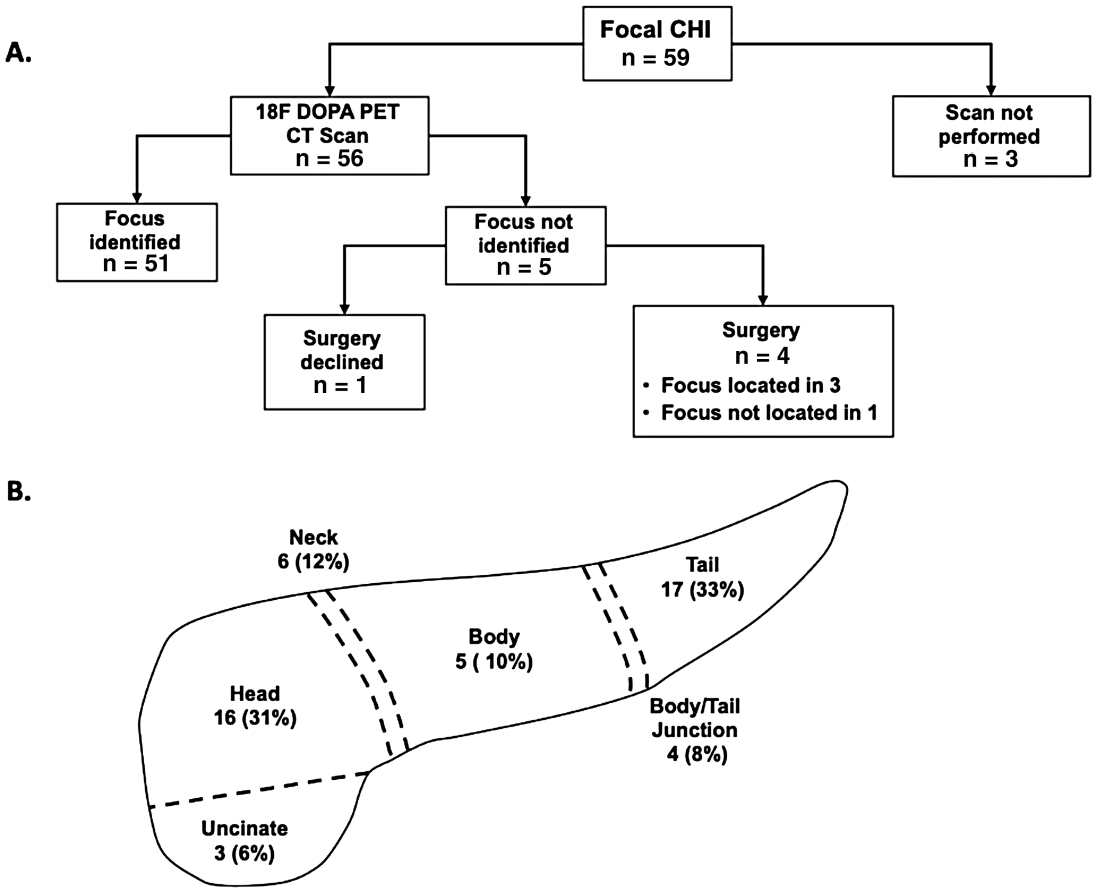

Figure 1. [18]F-DOPA PET CT scan outcomes and focal CHI location distribution within the pancreas. (A) Fifty-six patients underwent [18]F-DOPA PET CT with focal lesions identified by localized isotope retention in 51 (91%) patients. Three patients did not undergo scan due to unavailability of scanning facilities. A focus was not clearly identified in 5 (8.9%) patients. Of these, a focal lesion was identified on frozen section histopathology in 3 patients, 1 patient had negative histopathology, and the remaining 1 patient declined surgical exploration. (B) Focal lesions were present evenly throughout the pancreas with similar frequencies.

Table 2. Medical management of postoperative hypoglycemia in focal CHI

Patient ID	Surgery extent	Number of surgeries	Medication/Carbohydrate supplementation	Duration, years
44	Subtotal	2	Diazoxide	4.2
45	Extended	3	Lanreotide	Ongoing
46	Focal Lesionectomy	1	Octreotide	4.6
47	Extended	1	Carbohydrate supplement	3.0
48	Subtotal	2	Carbohydrate supplement	4.0
49	Extended	1	Octreotide	3.0

Extent of pancreatectomy, treatment type, and age at hypoglycemia resolution are shown for the 6 patients requiring treatment for hypoglycemia after surgery. Surgery was defined as subtotal pancreatectomy ("Subtotal"), "Lesionectomy," and extended focal surgery ("Extended"). One patient continues to require therapy 5 years after surgery

initial surgery (2 focal lesionectomy; 5 extended focal surgery; 3 subtotal), of whom 7 underwent further surgery and 3 were managed with medication or high-concentration carbohydrate feed supplementation (Fig. 2 and Table 2). Subsequent surgery was successful in 4 patients while 3 continued to have hypoglycemia requiring medical therapy. In the 6 patients with persistent postoperative hypoglycemia, treatment was required for a median 4.0 years after surgery (range 3.0-4.6) in 5 patients and therapy continues to be required in 1 patient 5 years after surgery (Table 2). This patient underwent a third operation but continued to experience hypoglycemia postoperatively. They were switched to lanreotide at 9 months of age and the interval between lanreotide doses has increased to 5 to 6 weeks with maintenance of fasting tolerance of 18 hours and no occurrence of hypoglycemic episodes with home glucose monitoring (Table 2).

Surgical complications occurred in 5 (9%) patients all of whom underwent lesionectomy. The complications were hepatobiliary in nature, involving laceration (n = 1), fluid collection (n = 2), and biliary strictures (n = 2). One patient who developed a bile duct stricture required choledochoduodenostomy. The others were conservatively managed with satisfactory surgical outcomes requiring no further intervention.

Table 3. Outcomes of medically managed patients with focal congenital hyperinsulinism

Patient ID	Reason for medical management	Medication	Age at discontinuation, years
50	Family declined	Diazoxide until 8 months Octreotide until 1.5 years	1.5
51	Surgical accessibility to lesion considered complex	Lanreotide	Ongoing
52	Family declined	Octreotide	2.8
53	Family declined	Octreotide	3.2
54	Focus not identified on biopsy	Octreotide	4.0
55	Focus not identified on biopsy	Octreotide	2.1
56	Focus not identified on biopsy	Octreotide	1.6
57	Family declined	Octreotide	7.7
58	Focus not identified on biopsy	Octreotide	1.8

The reason for medical management, medication and age at discontinuation are shown for 9 patients managed conservatively. This group includes the 4 patients in whom the focus could not be identified on frozen section biopsy and 1 patient surgical accessibility in the head was deemed challenging after biopsy (Fig. 1).

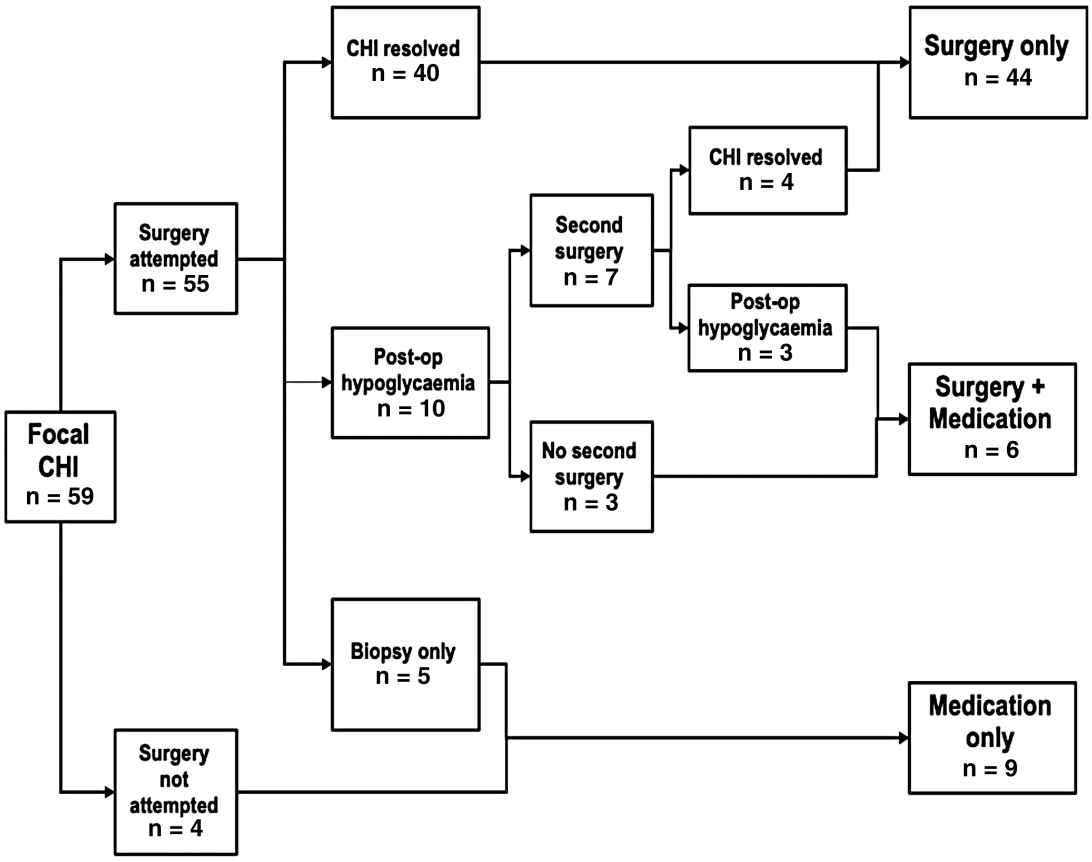

Figure 2. Surgical approach, outcomes, and definitive management for focal CHI patients, 2003-2018. Surgery was attempted in 55 (93%); surgery was declined by the family in 4 patients. Of the patients taken to surgery, 40 had successful resolution of CHI, 10 had postoperative hypoglycemia, and 5 patients underwent biopsy only (focal lesion not located in 4 and surgical accessibility in the head was deemed challenging based on frozen section biopsy in the remaining patient). Of the patients with hypoglycemia after initial surgery, 7 underwent second-look surgery with subsequent CHI resolution in 4 and ongoing hypoglycemia in 3 patients.

Three patients developed long-term complications related to pancreatic resection. One patient developed both diabetes and pancreatic insufficiency (PI) at 33 days and 1 year of age, respectively, following subtotal pancreatectomy. One patient developed diabetes but not PI at 11 years of age also postsubtotal pancreatectomy, while 1 developed PI at 9 months after undergoing a further 2 surgeries for persistent hypoglycemia (patient 45, Table 2). The extent of pancreatic resection was presumably the cause of the exocrine insufficiency in this patient.

Medically Managed Patients With Focal CHI

In 9 (15%) patients with focal CHI, surgery was not performed (Fig. 2). Five patients were brought to surgery, but

a focus was not identified on frozen section histology in 4 patients and surgical accessibility in the head was deemed challenging in the fifth patient. No further resection was performed. The other 4 patients declined surgery; this group included 1 patient in whom a focus was not clearly identified on ^{18}F-DOPA PET/CT scan. Euglycemia was achieved with octreotide treatment in 8 patients at a median dose of 17 µg/kg/day (range 12-40 µg/kg/day). The remaining patient was managed on a combination of diazoxide and octreotide due to partial responsiveness to both medications. Medication was discontinued in 8 (89%) patients at a median age of 2.4 (range 1.5-7.7) years (Table 3). The patient remaining on treatment transitioned to lanreotide at 11 years of age.

Neurodevelopmental Outcomes

Neurodevelopment was assessed in 33 (56%) patients; it was not possible to ascertain neurodevelopmental status in the remaining 26 patients through medical note review due to relative infrequent reviews in the postoperative period. Abnormal neurodevelopment was reported in a total of 13 (22%) patients, of whom 10 patients were managed with surgery alone, 1 required medication after surgery, and 2 were treated with medication alone.

In the patients managed with surgery alone, developmental delay (global or speech/language) was reported in 8 patients (including 2 with autistic features, 1 with seizures, and 1 with both seizures and visual impairment), 1 patient had epilepsy only, and the remaining patient had mild learning difficulties. The patient requiring medication after surgery had global delay and visual impairment. Neurodevelopmental assessment was available in only 2 patients managed with medication alone, both of whom had developmental delay. The seizures and visual impairment developed after surgery and/or medical management in all patients.

Discussion

To our knowledge, this is the largest study to date comparing outcomes of medically and surgically treated patients with focal CHI, evaluating a national cohort over a 15-year period. The treatment of choice for focal CHI remains surgical excision of the lesion based on already known data [1, 7]. Multiple studies have highlighted age-appropriate fasting tolerance and resolution of hypoglycemia after the removal of the focal lesion, ranging from 91.4% to 97% [14, 25, 33-35]. In our cohort, surgery was curative for 88% of those undergoing surgery.

It is accepted that surgical management of focal CHI is not always feasible and can be associated with suboptimal outcomes. Focal lesions in the pancreatic head abutting the biliary apparatus may be relatively inaccessible, while incomplete resection of lesions may lead to recurrence of hypoglycemia [7, 29, 36], which suggests that a nonsurgical approach might be considered in select patients with focal CHI. Our cohort study combining the experience of 2 national centers is the first to describe surgical complications and alternative conservative approaches in the management of focal CHI. While the majority of patients undergoing pancreatic surgery were "cured", a small proportion (9%) had complications, not dissimilar to those described previously [25].

In our cohort ^{18}F-DOPA PET/CT scan correctly identified a focal lesion in 91%, but in 9% of the cases scan results were discordant. In the latter group, scan results were either inconclusive or incorrectly localized foci, tallying with the results of a previous study [14]. Therefore, our study reinforces the need to interpret ^{18}F-DOPA PET/CT scan results with caution and the need to retain surgical and histopathological skills to correctly identify and localize focal lesions for optimal clinical outcomes.

There is some evidence that a small proportion of patients with focal CHI may respond, albeit partially to medical management [14, 27, 28]. Our data from a national cohort add to this evidence but do detract from the first-line option of surgery. In our cohort, 9 (15%) patients were managed by medical therapy for several reasons. In this group, 8 patients were able to discontinue medications at a median age of 2.4 years with satisfactory fasting tolerance suggestive of resolution of CHI. Our data support a trend to reducing severity of focal CHI disease over time in a small proportion of patients with focal CHI [33, 37]. These data may assist clinical discussion around optimal management strategies in patients with complex focal CHI where location of the lesion and surgical feasibility are uncertain. Additionally, both technical and technological advances in surgical management are important in improving curative outcomes in focal CHI. Intraoperative ultrasound for instance was recently shown to have 80% sensitivity and 100% specificity for focal CHI detection including identification of an ectopic lesion [38].

While our data represent the national experience from 2 specialist centers, given the retrospective nature of the study, outcome data were not uniformly available at both centers. Long-term outcomes were variably reported, impacting on data quality, including data on neurodevelopment. Given this and the small number of patients who underwent conservative vs surgical management, the data should be interpreted cautiously. Furthermore, it could not be ascertained if adverse neurodevelopment was a function of early-life hypoglycemia due to delayed diagnosis and/or hypoglycemia treatment, or a consequence of the risk of recurrent hypoglycemia through adherence to medical management.

In conclusion, our national experience reinforces surgical excision of the lesion as the treatment of choice for the treatment of focal CHI. In select patients with focal CHI, such as those in a difficult anatomical position, conservative nonsurgical approaches could be considered as treatment alternatives.

Funding

The study was supported by the Northern Congenital Hyperinsulinism (NORCHI) charitable fund, the NIHR Translational Collaboration award, and the Manchester Academic Health Sciences Centre, Great Ormond Street Hospital Charity (Hyperinsulinism fund).

Disclosures

None.

Data Availability

Statement: All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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