CASE SERIES

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Congenital Hyperinsulinism with Paternally Inherited *ABCC8* Variants: A Single Center Experience over a Decade in Singapore

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Abstract

ABCC8 pathogenic variants have been found to cause neonatal diabetes mellitus (NDM), maturity-onset diabetes of the young (MODY) and congenital hyperinsulinism (CHI), depending on the nature of the mutation. Few studies have reported on the carrier frequency of CHI-related *ABCC8* variants. In Singapore, the carrier rate is 1 in 754. Paternally inherited *ABCC8* recessive variants have been classically associated with focal lesions causing CHI.

In our case series of five patients with paternally inherited *ABCC8* variants, one patient had a second maternally inherited recessive variant, making him a compound heterozygous genotype presenting with severe, neonatal onset, diffuse disease that was not responsive to diazoxide. The remaining four patients had a single paternally inherited *ABCC8* variant, of which three were previously reported to be recessive variants—only 1 had a focal lesion while the rest had diffuse disease. A comprehensive review of our cases suggests that patients with paternally inherited *ABCC8* variants, whether autosomal recessive, heterozygous, or associated with genetic syndromes, were heterogenous in their clinical manifestations and cannot be reliably distinguished based on their initial clinical presentation.

A deeper understanding of the genotype-phenotype correlation of *ABCC8*-related CHI will require further research and functional analyses. Both a genetic diagnosis and imaging using ^{18}F-DOPA-PET should be pursued in a timely manner once diazoxide unresponsiveness has been established. Single-stage near-total pancreatectomy may be considered for patients with diffuse disease.

Key words: congenital hyperinsulinism, paternally inherited, ABCC8 gene, diazoxide, ^{18}F DOPA PET CT

INTRODUCTION

Neonatal diabetes mellitus (NDM), maturity-onset diabetes of the young (MODY) and congenital hyperinsulinism (CHI) form a spectrum of diseases that result from pathogenic variants in the *ABCC8* gene.[1] This gene encodes the sulphonylurea receptor (SUR1) subunit of the potassium adenosine triphosphate (K_{ATP}) channel involved in insulin synthesis within the pancreatic β-cell. A gain-of-function or loss-of-function mutation of the *ABCC8* gene leads to deficient or excessive insulin production, respectively.

The earliest report of CHI from loss-of-function *ABCC8* mutation dated back to 1995.[2] As the most severe form of hyperinsulinemic hypoglycemia (HH) in newborns, CHI is characterized by inappropriate secretion of insulin during an episode of hypoglycemia. Transient forms are commonly seen in infants of diabetic mothers, those born small or large for gestational age, or following perinatal stress. These cases are usually diazoxide-responsive and resolve without requiring long-term pharmacotherapy. When there is persistent severe hypoglycemia requiring high glucose infusion rates (GIR), patients should be evaluated for CHI. The most common genes responsible for CHI are the K_{ATP} channel regulating genes, *ABCC8* and *KCNJ11*, which lie on chromosome 11p15.1.[3,4] Variants in these genes lead to impaired K_{ATP} channel synthesis, defective trafficking within the cell and to the plasma membrane, or altered glucose sensitivity– resulting in persistent β-cell membrane depolarization and continuous insulin release,

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suppressing gluconeogenesis, glycogenolysis and lipolysis, culminating in non-ketotic hypoglycemia.[5,6] Timely diagnosis and management of CHI is important to prevent acute complications of hypoglycemia such as seizures and death, as well as long-term neurological sequelae including cerebral palsy.

The estimated incidence of CHI is between 1 in 27,000 and 1 in 50,000 live births, with higher incidences seen in communities that are isolated and with higher consanguinity rates.[7,8] Less is known regarding the carrier frequency of *ABCC8* variants. Still, Glaser et al. reported a mutation carrier rate of 1 in 52 amongst more than 21,000 Ashkenazi Jewish individuals who were genotyped, translating to an estimated incidence of 1 in 10,816 for homozygous or compound heterozygous *ABCC8*-related CHI.[9] Numerous studies have reported hundreds of pathogenic *ABCC8* variants to elucidate genotype-phenotype correlations in CHI.[7]

In a cohort study 300 CHI patients, Kapoor et al. identified 45.3% with a genetic diagnosis.[10] While majority of the diazoxide-responsive cases had no identifiable mutation, 92.8% of those unresponsive to diazoxide had either *ABCC8* or *KCNJ11* pathogenic variants. CHI patients with *ABCC8* variants may be homozygous, compound heterozygous or heterozygous. Most patients with homozygous or compound heterozygous mutations are diazoxide unresponsive and have diffuse disease. Those with heterozygous *ABCC8* mutations may exhibit diazoxide responsive or diazoxide unresponsive phenotypes. Majority of them are dominant mutations, but a smaller group of patients has been found to have paternally inherited *ABCC8* variants with clinically unaffected fathers.[10,11] Historically, paternally inherited *ABCC8* variants have been associated with focal lesions, with loss of heterozygosity of the maternal allele demonstrated within the focal disease region.[12,13] However, there have been rare reports of paternally inherited *ABCC8* variants (from unaffected fathers), without a second hit identified, resulting in diffuse disease.[14]

In this report, we describe five patients who have CHI with paternally inherited *ABCC8* variants. Three of the cases involve known recessive variants, and notably only one patient exhibited the classical association with a focal lesion while the others had diffuse disease. We discuss the possible reasons for the difference between what we found in our patients and that which has been previously reported. Our findings suggest that CHI arising from paternally inherited *ABCC8* variants present with different clinical phenotypes, thus highlighting the variability in genotype-phenotype correlation.

METHODOLOGY

Patient selection

We included patients diagnosed with CHI and paternally inherited *ABCC8* variants on genetic testing. These patients were either born at or transferred to our center, which has established a HH program since 2015. Each child fulfilled the biochemical criteria for HH and inherited *ABCC8* variants from their fathers.

Data collection

Data were collected retrospectively from electronic medical records. Relevant antenatal and birth history collected included birth gestational age, birth weight, delivery mode, presence of antenatal scan abnormalities, maternal gestational diabetes mellitus and consanguinity, the age at first documented hypoglycemia episode and accompanying symptoms. Biochemical parameters collected included plasma glucose, insulin, ketone, cortisol, free fatty acid and growth hormone levels. Radiological investigations, where available, included findings from ^{18}F-DOPA-PET scan. Treatment-related information was noted, including maximum GIR, age at initiation and maximum doses of oral diazoxide, subcutaneous octreotide and oral nifedipine. For patients who underwent surgery, the procedure performed and estimated percentage of pancreas removed were recorded. Long-term comorbidities and neurodevelopmental outcomes were documented from outpatient follow up records.

Genetic testing

Genetic testing was performed using blood samples collected in EDTA tubes. Patients 1, 2 and 3 underwent Invitae Hypoglycemia Panel testing (San Francisco, CA, USA, Test Code 98006, includes 120 genes); while patients 4 and 5 underwent Sanger sequencing of the *ABCC8* and *KCNJ11* genes at Exeter Molecular Genetics Laboratory (UK).

All patients underwent comprehensive genetic counseling provided by a trained genetic counsellor in collaboration with geneticist. A written informed consent was obtained from a parent before testing. Genetic test results were reviewed by a geneticist before discussion with patient's family. In cases where a pathogenic variant was identified, further parental testing was conducted to determine if the mutation was inherited or *de novo*.

Ethical considerations

The study was granted exemption from review and informed consent by the SingHealth Institutional Review Board (CIRB 2021/2166) due to its use of de-identified clinical data.

CASE

We present five patients who were diagnosed with CHI with paternally inherited *ABCC8* variants. Table 1 shows the patients' demographic and relevant perinatal information. Four of them were male and four were Asians. All were born to non-consanguineous parents. One patient was

Table 1. Patient's demographic information

Patient	1	2	3	4	5
Sex	Male	Female	Male	Male	Male
Ethnicity	Asian	Asian	Asian	Non-Asian	Asian
Gestational age (Weeks + days)	37+3	36+6	39+5	37+5	38+5
Birth weight (g), SDS, centile (%)	5038, +4.14, 100	4575, +3.30, 99.9	4585, +2.17, 99.5	3335, +0.73, 77.0	3230, -0.16, 50
Mode of delivery	LSCS	LSCS	LSCS	NVD	LSCS
Antenatal scan abnormality	Macrosomia	Macrosomia	Macrosomia	None	None
Gestational diabetes (Yes/No)	No	Yes	No	No	No
Parental consanguinity (Yes/No)	No	No	No	No	No

LSCS, lower section cesarean section; NVD, normal vaginal delivery

Table 2. Patient's biochemistry and radiological investigations results

Patient	1	2	3	4	5
First hypoglycemia					
Hours of life	2	6	Day 93	36	3
Symptomatic (Yes/No)	No	No	Yes	Yes	Yes
BG (mmol/L)	2.0	2.7	2.8	1.5	0.2
Critical blood samples					
Days of life	Day 3	Day 6	93	Day 18	Day 3
BG (mmol/L)	1.5	2.7	2.8	2.5	1.2
Ketones (mmol/L)	0.1	0	0.3	0.0	(N.D.)
Insulin (mU/L)	89.7	52.4	3	3.3	11.7
Free fatty acid (mmol/L)	<0.10	0.11	1.7	(N.D.)	(N.D.)
Imaging results					
^{18}F-DOPA scan	Diffuse	Diffuse	Diffuse	Focal	
^{68}G-DOTATATE-PET					Inconclusive
^{68}GA-NODAGA-Exendin-4 scan	No focal lesion				
Ultrasound					Small nodular focus at junction of pancreas body and medial tail
Pancreatectomy	Near total	Subtotal at 3-month-old Near total at 5-month-old	No surgical intervention	Focal lesionectomy	Partial at 4-month-old Near total at 6-month-old

BG, blood glucose; N.D., no data

born late preterm at 36 + 6 weeks gestation, while the rest were term. Their birth weights ranged between 3,230 g and 5,038 g; three of the patients were macrosomic and required delivery by caesarean section, while the other two had birth weight appropriate for gestational age. Only one patient was an infant of mother with gestational diabetes.

Results of the diagnostic evaluation and treatment information of each patient are presented in Tables 2 and 3, respectively. All except one child presented with hypoglycemia early, within the first 48 hours of life, with blood glucose ranging between 0.2 to 2.0 mmol/L. Half of these patients were symptomatic, and all of them required high GIR (16.4 to 26.6 mg/kg/min) to maintain normoglycemia. These four patients were treated with oral diazoxide at doses up to 15-20 mg/kg/day and subcutaneous octreotide 33-35 mcg/kg/day but continued to have persistent hypoglycemia. The child (Case 3) who presented later at 3 months of life was born in an external medical facility and early postnatal glucose levels were reportedly normal. He required a relatively lower GIR and was the only case who responded to diazoxide at the dose of 4.5 mg/kg/day.

Four patients underwent ^{18}F-DOPA scan, while one underwent ^{68}G-DOTATATE PET scan due to the unavailability of the ^{18}F-DOPA scan in our center at the time when the first case of CHI was diagnosed. Out of the four patients who underwent ^{18}F-DOPA scan, three showed diffuse disease and only one demonstrated a focal lesion that was typically associated with paternally inherited *ABCC8* variant.

Patients who were diazoxide-unresponsive and had diffuse disease were eventually managed with near total pancreatectomy, while the patient with a focal lesion underwent curative lesionectomy.

Case 3, the only patient who responded to diazoxide, was also found to have a pathogenic *ABCC9* variant and had clinical features consistent with Cantu Syndrome – coarse facial features, hypertrichosis, large patent ductus arteriosus, complex subarachnoid vasculature and a left-sided congenital pulmonary airway malformation. He was recently admitted with persistent hypoglycemia following a viral gastrointestinal illness which required careful titration of diazoxide to 7 mg/kg/day, without cardio-

Table 3. Pharmacological interventions and follow-up outcomes

Patient	1	2	3	4	5
Treatment from diagnosis					
Maximum GIR (mg/kg/min)	21	26.6	8.8	20	16.4
Diazoxide					
Days of life initiated	10	7	102	12	3
Initial dose (mg/kg/day)	4.8	5.3	3.0	5.0	6.0
Maximum dose (mg/kg/day)	15.0	11.0	4.5	20.0	20.0
Octreotide					
Days of life initiated	44	14	Nil	19	45
Initial dose (mcg/kg/day)	5.0	5.2		5.0	7.5
Maximum dose (mcg/kg/day)	33.0	33.0		35.0	33.0
Nifedipine					
Days of life initiated		74			65
Initial dose (mg/kg/day)		1.1			0.2
Maximum dose (mg/kg/day)		1.26			0.7
Treatment on discharge					
Diazoxide (mg/kg/day)			4.5		
Hydrochlorothiazide (mg/kg/day)			4.5		
Octreotide (mcg/kg/day)					10
Mode of feeding	Gastrostomy	Gastrostomy	Oral + NGT	No data	NGT
Follow up					
Age at time of writing in years	0.7	1.5	2	8	13
Neurodevelopment	Normal	Normal	Normal	Normal	Normal

GIR, glucose infusion rate; NGT, nasogastric tube feeding

Table 4. Genetic variant found in relation to clinical phenotype of CHI

Patient	1	2	3	4	5
First variant found	*ABCC8* c.4258C>T (p.Arg1420Cys)	*ABCC8* c.4400C>T (p.Pro1467Leu)	*ABCC8* c.4252C>T (p.Arg1418Cys)	*ABCC8* c.4480C>T (p.Arg1494Trp)	*ABCC8* c.4414G>A (p.Asp1472Asn)
Classification	Heterozygous pathogenic	Heterozygous, VUS	Heterozygous Likely pathogenic	Heterozygous pathogenic	Heterozygous pathogenic
Inheritance	Paternal	Paternal	Paternal	Paternal	Paternal
Other variant found	*ABCC8* Partial deletion on Exon 31	None	*ABCC9* c.3347G>A (p.Arg1116His)	None	None
Classification	Heterozygous pathogenic		Heterozygous pathogenic		
Inheritance	Maternal		*De novo*		
Pancreas involvement	Diffuse	Diffuse	Diffuse	Focal	Diffuse
Diazoxide response	Resistant	Resistant	Responsive	Resistant	Resistant
Age at diagnosis	Day 3	Day 6	Day 93	Day 2	Day 3
Surgical intervention	Near total pancreatectomy	Near total pancreatectomy	Nil required	Lesionectomy	Near total pancreatectomy
Risk of recurrence in next offspring	25%	Uncertain	Uncertain	Negligible	Uncertain

VUS, variant of uncertain significance

vascular compromise. Following recovery, diazoxide dose was weaned back to baseline.

Table 4 summarizes the salient clinical features of each patient in relation to their genetic variant. Each patient had a distinct paternally inherited *ABCC8* variant. One patient had a concomitant maternally inherited partial deletion of the *ABCC8* exon, which makes him a compound heterozygous genotype. Out of the four patients who had a single paternally inherited *ABCC8* variant – one was diazoxide-unresponsive and had a focal lesion, two were diazoxide-unresponsive and had diffuse disease, while the last one was diazoxide-responsive and had diffuse disease.

As of this writing, the patients are now between 8 months old and 13 years of age and remain on follow-up. All of them have normal neurodevelopmental outcomes thus far.

DISCUSSION

Reference genomic data from Singapore's National Precision Medicine (NPM) program has shown that the carrier rate of an *ABCC8* gene mutation in our local population is 1 in 754 and the carrier frequency is similar in both genders.[15] The average number of live births per year in Singapore in the past decade (between 2014 and 2023) was 31,000.[16] This translates to 41 new carriers of the *ABCC8* mutation each year. To the best of our knowledge, the five patients reported in this case series are the only documented cases of CHI with paternally inherited *ABCC8* variants in our country over the past decade. While most carriers are likely to have a recessive variant, some of the CHI-related paternally inherited *ABCC8* variants may be dominant forms with variable penetrance – a possible explanation accounting for CHI patients with only a single paternally

inherited *ABCC8* variant detected and asymptomatic fathers.

When managing a patient with CHI, determining diazoxide-responsiveness is a crucial step. Patients who do not respond to diazoxide may require somatostatin analogs (octreotide), but tachyphylaxis and suboptimal compliance due to multiple injections limit its acceptability and efficacy.[17] Surgical intervention may hence become inevitable to prevent recurrent hypoglycemia and its undesirable consequences, including neuro-disability. In such cases, genetic testing and imaging of the pancreas are key investigations that guide further management. Genetic forms of CHI are unlikely to resolve over time and are often resistant to diazoxide, unlike cases with an identified pathogenic variant.[17,18] ^{18}F-DOPA-PET is the imaging of choice to differentiate focal lesions from diffuse disease.

Focal lesions can be treated with a lesionectomy which is often curative. Post-operative complications are minimal and most patients maintain normoglycemia without requiring further medical intervention.[17,19-21] Diffuse disease often requires near-total pancreatectomy and has far less satisfactory post-operative outcomes. Some of these patients continue to experience hypoglycemia despite having most of their pancreas removed due to persistent overactivity of remnant β-cell – necessitating continued pharmacotherapy or even additional surgery.[6] Majority eventually develop post-pancreatectomy diabetes mellitus and exocrine insufficiency.[22-24]

Numerous studies have explored the genotypic-phenotypic correlation in CHI, as it has several important clinical implications. Understanding these correlations may i) allow us to anticipate the clinical behavior of the CHI based on genetic results and manage them pro-actively, ii) aid in prenatal or antenatal counseling for individuals who are carriers and planning to conceive,[6] and iii) in resource-limited regions, surgical intervention may potentially be pursued without the absolute need for advanced imaging techniques (such as ^{18}F-DOPA-PET) which can be a logistical challenge that significantly delays definitive treatment.

Paternally inherited *ABCC8* heterozygous mutations have been classically associated with focal pancreatic lesions. In this study, we presented five CHI cases with paternally inherited *ABCC8* variants, with varying clinical characteristics. Of these cases, only one patient (patient 4) had a focal lesion, while the others had diffuse disease.

Patient 1 had a paternally inherited recessive missense *ABCC8* variant (c.4258C>T, p.Arg1420Cys),[25] as well as a maternally inherited recessive *ABCC8* variant that results in a partial deletion on exon 31 that is expected to disrupt RNA splicing and lead to loss of protein function. The latter is a novel variant that has not been previously reported. His clinical progress was consistent with what is expected of CHI arising from compound heterozygous recessively acting *ABCC8* mutations – diffuse disease with no response to diazoxide.[18] These patients tend to present early and have very recurrent hypoglycemia. In the case series by Kapoor et al., the median age of presentation for this genotype group was 1 day old. Between CHI patients with normal and poorer neurodevelopmental outcomes, the latter group was found to have significantly longer duration of intravenous glucose treatment and more severe symptoms at onset.[17] These patients invariably have diffuse disease and imaging may not be feasible or necessary especially in resource-limited settings.[6] Following knowledge of the genetic diagnosis, near total pancreatectomy may benefit the patients by avoiding further hypoglycemia and prolonged hospitalization.

Patients 2 and 5 had paternally inherited heterozygous *ABCC8* mutations, demonstrated no response to diazoxide, their ^{18}F-DOPA scan did not show any focal disease, and histopathological examination of their pancreas were conclusive of diffuse disease. Patient 2 had a missense variant of uncertain significance (c.4400C>T, p.Pro1467Leu) that had not been previously reported, while patient 5 had a missense variant (c.4414G>A, p.Asp1472Asn) that had been previously reported to be recessively acting.[14] Both patients' fathers carried the respective variants but were asymptomatic. Although paternally inherited recessive *ABCC8* variants are classically associated with focal lesions, both our patients had diffuse disease. Kapoor et al. had reported 6 out of 19 paternally inherited recessive *ABCC8* variants that were associated with diffuse disease, while another case series by Nessa et al., reported 3 out of 10 in their cohort. The exact mechanism that results in this phenomenon is unclear but possible explanations could include incomplete penetrance, presence of a second somatic recessive mutation within the pancreas that was not identified by sequencing, presence of other unknown genetic mutation (considering only around half of all CHI cases tested have an identifiable genetic mutation), or environmental influences.[12,13] We acknowledge our limitation which is the absence of further sequencing (such as Whole Genome Sequencing) to interrogate the intronic regions of CHI-related genes, that may potentially identify a second recessive variant. A less likely possibility would be a missed focal lesion at surgery.

Of note, the clinical presentations of patients 2 and 5 were not different from that of patient 1 (compound heterozygote) and patient 4 (focal disease). They presented with similar degrees of hypoglycemia within first few days of life and were not responsive to diazoxide or octreotide. A subtotal (80%) pancreatectomy was performed in both cases, with persistence of hypoglycemia post-operatively and they eventually went for second surgery to remove up to 95% of the pancreas. Both patients have normal neurodevelopmental outcomes to date.

Patient 3 was found to carry a paternally inherited recessive *ABCC8* variant (c.4252C>T, p.Arg1418Cys) and a *de novo* dominant *ABCC9* variant. The latter results in Cantu Syndrome, a rare autosomal dominant disease that occurs

from a gain-of-function mutation in the *ABCC9* or *KCNJ8* gene, that encode the SUR2 and Kir6.1 subunits of the K_{ATP} channels respectively. While SUR1 is mainly expressed by pancreatic β-cell, SUR2 is found in cardiac, skeletal and smooth muscles. Increased K_{ATP} channel activity renders the cell in hyperpolarized state, leading to reduced excitability and contraction of the muscle cell. The clinical features of Cantu syndrome include cardiomegaly, large patent ductus arteriosus, pulmonary hypertension, vascular tortuosity in brain and retina, generalized edema, skeletal abnormalities, hypertrichosis, coarse facial features and developmental delay.[26] There is currently no pharmacotherapy found effective in treating patients with Cantu syndrome, although glibenclamide, a sulphonylurea that inhibits SUR1/2 activity, had been discussed as a potential drug.[27] Of note, the use of diazoxide can be potentially harmful for patients with Cantu Syndrome because it works to increase K_{ATP} channel activity. This makes our case exceptionally interesting, because our patient has CHI resulting from coexisting *ABCC8* variant and he is diazoxide-responsive. Although this is a paternally inherited recessive variant from an unaffected father, it behaves atypically with a later onset, diffuse disease and was responsive to diazoxide. It is unclear whether the co-existence of the *ABCC9* variant has a role to play in contributing to its diazoxide-responsiveness. It is also with caution that diazoxide is used in the treatment of this patient's CHI, as close surveillance is required to ensure that the cardiovascular status of this child is not compromised.

CHI has been found to be associated with several genetic syndromes, but the mechanism through which the genetic defect results in dysregulation of insulin secretion and glucose metabolism are unclear in most. The syndromes that have been reported with CHI include overgrowth syndromes like Beckwith-Wiedemann and Sotos syndrome; monogenic developmental disorders such as Kabuki, Costello and CHARGE syndrome; chromosomal disorders such as Turner, Trisomy 13 and Trisomy 21; channelopathies like Timothy syndrome and Long QT; and metabolic disorders including congenital disorder of glycosylation, tyrosinemia and others.[28] To our knowledge, ours is the first case of Cantu Syndrome with CHI.

Patient 4 had a paternally inherited recessive *ABCC8* variant (c.4480C>T, p.Arg1494Trp)[29,30] that has been previously reported in several cases of focal CHI where loss of heterozygosity of the corresponding maternal allele was demonstrated. His clinical presentation and findings were consistent with what has been observed.

A comprehensive review of our cases suggests that patients with paternally inherited *ABCC8* variants, whether autosomal recessive, heterozygous or associated with genetic syndromes, are heterogenous in clinical phenotypes and cannot be reliably distinguished by their initial clinical presentation. Smith *et al.* described a pair of siblings with CHI who had the same paternally inherited *ABCC8* variant - the older sibling presented with persistent hypoglycemia that required GIR of 20.8 mg/kg/min and diazoxide, while the younger sibling had only transient hypoglycemia that resolved without high GIR requirement nor diazoxide.[31] Chang et al. presented 8 Chinese patients with CHI from *ABCC8* variants (most of them were paternally inherited heterozygous mutations with unaffected fathers) with variable clinical manifestations, suggesting that allelic expression imbalance (AEI) may be the underlying explanation for the phenotypic variations.[32]

Diazoxide-resistant disease may have focal or diffuse disease and can only be differentiated by functional imaging. Some focal lesions may still be missed on imaging.[21] While we acknowledge our limitations in the extent of genetic testing and the possibility of undiscovered CHI-causing mutations, paternally inherited heterozygous *ABCC8* variants do not necessarily indicate focal disease. Hence interpretation of ^{18}F-DOPA scan must be objective and unbiased. Furthermore, rare cases of CHI with multifocal lesions have been reported and curative treatment require removal of all the focal lesions.[33] This underscores the importance of pre- and intra-operative disease localization and careful planning of the surgical approach. A single-stage laparoscopic near-total pancreatectomy is the surgery of choice for these patients, as a subtotal pancreatectomy is unlikely to be successful in eliminating hypoglycemia in those with diffuse disease.

CONCLUSION

Patients with single paternally inherited *ABCC8* variants identified have variable clinical manifestations. They can have diffuse disease and may demonstrate diazoxide response. Their clinical presentations may not be distinguishable from the autosomal recessive, compound heterozygous, autosomal dominant or syndrome-associated forms of CHI. In this paper, we described cases of paternally inherited heterozygous *ABCC8* mutations with diffuse disease including one with a novel variant; a case with coexisting paternally inherited *ABCC8* and *ABCC9* variants with competing molecular mechanisms that have implications on medical therapy; and a case of compound heterozygous *ABCC8* mutations with a novel variant. Deeper understanding of the molecular mechanisms with functional analyses may help give us more information on the genotypic-phenotypic correlation in CHI cases related to *ABCC8*. From our experience, we advocate for prompt pursuit of a genetic diagnosis once diazoxide resistance is established or if there are atypical features (i.e., syndromic), followed by timely imaging with ^{18}F-DOPA-PET scan to detect focal or diffuse disease, and a single-stage near-total pancreatectomy may be considered in cases of diffuse disease. With this approach, we can avoid prolonged hospitalization and recurrent hypoglycemia and optimize neurodevelopmental outcomes in these patients.

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Patients' consent were obtained before submission of the manuscript.

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Datasets generated and analyzed are included in the published article.

CRediT Author Statement
CC: Conceptualization, Methodology, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **DC:** Conceptualization, Conceptualization, Resources, Data Curation, Writing – review and editing, Visualization, Project administration; **ALK:** Writing – review and editing, Visualization; **SC:** Conceptualization, Formal analysis, Resources, Data curation, Writing – review and editing, Visualization, Supervision, Project administration; **FY:** Conceptualization, Formal analysis, Resources, Data curation, Writing – review and editing, Visualization, Supervision, Project administration.

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