CLINICAL STUDY

The contribution of rapid K_{ATP} channel gene mutation analysis to the clinical management of children with congenital hyperinsulinism

I Banerjee¹, M Skae¹, S E Flanagan², L Rigby¹, L Patel¹, M Didi³, J Blair³, S Ehtisham¹, S Ellard², K E Cosgrove^{4,5}, M J Dunne^{4,5} and P E Clayton^{1,4}

¹Department of Paediatric Endocrinology, Royal Manchester Children's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Oxford Road, Manchester M13 9WL, UK, ²Peninsula Medical School, Institute of Biomedical and Clinical Science, University of Exeter, Exeter EX2 5DW, UK, ³Department of Paediatric Endocrinology, Alder Hey NHS Foundation Trust, Liverpool L12 2AP, UK and ⁴Manchester Academic Health Sciences Centre and ⁵Faculty of Life Sciences, University of Manchester, Manchester M13 9NT, UK

(Correspondence should be addressed to I Banerjee; Email: indi.banerjee@cmft.nhs.uk)

Abstract

Objective: In children with congenital hyperinsulinism (CHI), K_{ATP} channel genes (*ABCC8* and *KCNJ11*) can be screened rapidly for potential pathogenic mutations. We aimed to assess the contribution of rapid genetic testing to the clinical management of CHI.

Design: Follow-up observational study at two CHI referral hospitals.

Methods: Clinical outcomes such as subtotal pancreatectomy, ¹⁸F-Dopa positron emission tomography–computed tomography (PET–CT) scanning, stability on medical treatment and remission were assessed in a cohort of 101 children with CHI.

Results: In total, 32 (32%) children had pathogenic mutations in K_{ATP} channel genes (27 in *ABCC8* and five in *KCNJ11*), of which 11 (34%) were novel. In those negative at initial screening, other mutations (*GLUD1*, *GCK*, and *HNF4A*) were identified in three children. Those with homozygous/compound heterozygous *ABCC8/KCNJ11* mutations were more likely to require a subtotal pancreatectomy CHI (7/10, 70%). Those with paternal heterozygous mutations were investigated with ¹⁸F-Dopa PET–CT scanning and 7/13 (54%) had a focal lesionectomy, whereas four (31%) required subtotal pancreatectomy for diffuse CHI. Those with maternal heterozygous mutations were most likely to achieve remission (5/5, 100%). In 66 with no identified mutation, 43 (65%) achieved remission, 22 (33%) were stable on medical treatment and only one child required a subtotal pancreatectomy.

Conclusions: Rapid genetic analysis is important in the management pathway of CHI; it provides aetiological confirmation of the diagnosis, indicates the likely need for a subtotal pancreatectomy and identifies those who require ¹⁸F-Dopa PET–CT scanning. In the absence of a mutation, reassurance of a favourable outcome can be given early in the course of CHI.

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Background

The K_{ATP} channel, comprising four outer sulphonylurea receptor (SUR1) subunits and four inner potassium inward rectifying pore (Kir6.2) subunits encoded by the genes *ABCC8* and *KCNJ11*, is a major regulator of insulin release in the β cell of the pancreas. Congenital hyperinsulinism (CHI) is a rare disease causing hypoglycaemia but is one of the commonest causes of persistent hypoglycaemia in children. CHI is a heterogeneous condition with a significant genetic component (1, 2). Of the various genetic mechanisms identified, K_{ATP} channel gene mutations represent a major cause for the disease (1, 3–5), although other mutations have also been described (3–8). Mutation testing of

ABCC8/KCNJ11 is now possible with a rapid turnaround time of <10 days; therefore, rapid genetic analysis of the K_{ATP} channel genes has the potential to be important for several aspects of CHI therapy, from genetic counselling to the differential diagnosis of focal and diffuse disease and the likelihood of remission (3, 6, 8). The profiles of K_{ATP} channel gene mutations have been reported in some cohorts, especially in relation to medical and surgical treatment (9–12), but the utility of rapid genetic analysis on the clinical outcomes at follow-up in children with CHI remains to be defined. There is a need to understand the relevance of rapid K_{ATP} channel gene mutation analysis at diagnosis and whether they inform the probability of various clinical outcomes in children with CHI.

Aim

In this study, we aimed to investigate the utility of rapid K_{ATP} channel mutation analysis at diagnosis in contributing to the following clinical management outcomes:

- subtotal pancreatectomy for non-focal CHI,
- requirement for ^{18}F -Dopa positron emission tomography–computed tomography (PET–CT) scanning to diagnose focal CHI,
- likelihood of achieving stability on medical therapy and
- likelihood of remission.

Methods

A cohort of 101 children with CHI presenting to a regional centre in the North of the UK (Northern Congenital Hyperinsulinism Service, at the Royal Manchester Children's Hospital and Alder Hey Children's Hospitals) was reviewed. Local ethical approval was obtained for the study. Patients were prospectively recruited between 2006 and 2010. In patients presenting to the service prior to 2006, recruitment was retrospective.

The diagnosis of CHI was confirmed if serum insulin was detectable (>2 mU/l) at the same time as hypoglycaemia (blood glucose <2.6 mmol/l), along with concomitant evidence of elevated glucose requirement (>8 mg/kg per day) at least twice over a period of 24 h, a lack of urinary ketosis and the absence of underlying factors such as infection, metabolic disease or exogenous hypoglycaemic agents (4, 13–15). Neonates with a history of perinatal asphyxia were excluded from this study. Children with birth weight <2 nd centile for gestational age were also excluded from this study, unless diazoxide treatment was continued for 4 weeks or more, indicating persistent hyperinsulinism. Children with birth weight between 2nd and 9th centile were included in this study.

All children underwent rapid K_{ATP} channel mutation analysis for the *ABCC8* and the *KCNJ11* genes, with a turnaround time within ten working days of receipt of DNA from patients and their parents. If K_{ATP} channel mutation analysis was normal, the *GLUD1*, *HNF4A* and/or *GCK* genes were analysed with a turnaround time of 4–6 weeks from the receipt of DNA. *GLUD1* was sequenced in those children with marginally elevated serum ammonia levels suggestive of hyperinsulinism–hyperammonaemia, whereas *GCK* mutation analysis was undertaken if there was a dominant family history of hypoglycaemia and presentation was later than the neonatal period. Furthermore, *HNF4A* mutation testing was performed if a child was large for gestational age at

birth and there was a dominant family history of hyperglycaemia or diabetes.

Genomic DNA was extracted from peripheral leukocytes using standard procedures. All coding exons and exon/intron boundaries of *ABCC8*, *KCNJ11*, *GCK* and *HNF4A* genes and exons 6, 7, 10, 11 and 12 of the *GLUD1* gene were PCR amplified, purified and sequenced. Unidirectional sequencing was performed using universal M13 primers and a Big Dye Terminator Cyclase Sequencing Kit v3.1 (Applied Biosystems, Warrington, UK) according to the manufacturer's instructions. Reactions were analysed on an ABI 3730 Capillary sequencer (Applied Biosystems) and sequences were compared with the reference sequences (NM_000525, NM_000352.2 (which incorporates the alternatively spliced amino acid in exon 17 (L78224)), M37154, NM_000457.3 and NM_000162) using Mutation Surveyor v3.24 (SoftGenetics, State College, PA, USA). When a mutation was identified, parents were tested to establish the mode of inheritance, and microsatellite analysis (PowerPlex 16 System, Promega) was undertaken to confirm *de novo* mutations. When a single heterozygous recessively acting *ABCC8* mutation was identified in a patient with diffuse disease and there was sufficient DNA, dosage analysis of the *ABCC8* gene was performed using multiplex ligation-dependent probe amplification (MLPA) as per the manufacturer's instructions (MRC Holland, Amsterdam, The Netherlands, Kit P117-B1).

The clinical management of children with CHI was followed as per the protocol shown in Fig. 1. Children with CHI were considered to be diazoxide responsive if satisfactory glycaemic control was achieved with doses of oral diazoxide not exceeding 20 mg/kg per day and oral chlorothiazide not exceeding 15 mg/kg per day. Children were considered to be in remission either if no medication was required or if medication was stopped and no further medication or surgery was required to

Figure 1 Flowchart of investigation and management of children with CHI.

maintain stable glycaemic status for at least 3 months. In the case of the latter, the date for entering remission was the date at which medication was stopped. Dietary carbohydrate supplements were not classed as medication.

^{18}F -Dopa PET-CT scan was performed in those children with CHI with paternal heterozygous K_{ATP} channel mutations and in those who were mutation negative but remained persistently on medication, either diazoxide (with or without chlorothiazide) or octreotide for at least 3 months after diagnosis. The diagnosis of focal CHI was made on PET-CT scan by identifying a single focus with standardised uptake value > 1.5 in the focal lesion relative to the rest of the pancreatic tissue (16). Those without definite focal aetiology and those not requiring ^{18}F -Dopa PET-CT scanning were termed non-focal CHI (likely diffuse pancreatic lesions).

Data was analysed using SPSS 16.0 statistical software (SPSS, IBM Corporation, Somers, NY, USA). χ^2 tests were used to test for difference in proportions. Forward logistic regression was used to quantify probability of a variable when controlling other associated factors. Correlation was considered significant if probability (P) values were < 0.05 .

Results

A total of 101 children (69 males and 32 females), with a diagnosis of CHI at median (range) age 1 day (1 day, 1.6 years) and followed up for 2.3 (0.5–14.7) years, were reported in this study. The diagnostic serum insulin and C-peptide levels at the time of

hypoglycaemia were 12.8 (2.7–71.3) mU/l and 980 (249–5630) pmol/l, respectively, which confirmed biochemical evidence for hyperinsulinism.

Genetic analysis

In our cohort, 27 (26% of cohort) children were positive for *ABCC8* mutations and five (5% of cohort) children were positive for *KCNJ11* mutations on rapid K_{ATP} channel gene mutation analysis. A *GCK* mutation was identified in one proband and his/her father who had been asymptomatic but needed to consume extra carbohydrate during strenuous exercise. An *HNF4A* mutation was identified in a proband and his/her mother who had gestational diabetes during pregnancy and a *de novo* *GLUD1* mutation was identified in a single patient. No mutations were found in 66 children (65%) in our cohort.

In those who were positive for *ABCC8* mutations, 18 were heterozygous (11 paternal, three maternal and four *de novo*) and nine were either homozygous or compound heterozygous. There were 11 novel *ABCC8* mutations that were considered to be pathogenic (Table 1). These mutations affected amino acid residues that are conserved throughout evolution or resulted in a different amino acid substitution at a known mutation site. In one patient (patient #8, Table 1), a homozygous mutation was identified at position +5 of the conserved splice donor site of intron 9, and *in silico* analysis predicted that this mutation would affect splicing (www.fruitfly.org). None of the novel mutations had been identified in a cohort of 800 patients with the opposite phenotype of diabetes (Ellard & Hattersley, unpublished data). All mutations except one (patient #5, Table 1)

Table 1 Characteristics of novel K_{ATP} channel gene mutations detected in children with CHI. Sequence information is based on the GenBank reference sequences, NM_000525 for *KCNJ11* and NM_000352.2 for *ABCC8*, which incorporates the alternate exon 17 (GenBank L78208, L78224) that contains an additional amino acid. Numbering is based on +1 as the A of the major start codon of exon 1.

Patient	Gene	Mutation (nucleotide)	Mutation (protein)	Inheritance	Response to diazoxide
#1	<i>ABCC8</i> Exon 1	c.107A>G	p.His36Arg	Compound heterozygote: maternal and paternal	U
#2	<i>ABCC8</i> Exon 1	c.11C>T	p.Ala4Val	Presumed paternal	U
#3	<i>ABCC8</i> Exon 2	c.208G>A	p.Gly70Arg	Compound heterozygote: maternal and paternal	U
#4	<i>ABCC8</i> Exon 37	c.4547C>T	p.Thr1516Met	Heterozygous maternal	R
#5	<i>ABCC8</i> Exon 34	c.4169T>G	p.Leu1390Arg	<i>De novo</i>	R
#6	<i>ABCC8</i> Exon 10 Exon 33	c.1562G>C and c.4079C>T	p.Arg521Pro p.Pro1360Leu	Compound heterozygote: maternal and paternal	U
#7	<i>ABCC8</i> Exon 21	c.2525G>A	p.Arg842Gln	Paternal heterozygote	U
#8	<i>ABCC8</i> Intron 9	c.1467+5G>A	p.?	Homozygous	U
#9	<i>ABCC8</i> Exon 35	c.4287del	p.Val1430fs	<i>De novo</i>	U
#10	<i>ABCC8</i> Exon 4 Exon 13	c.512dup and c.?–1818_1923+?del	p.Thr172fs and p.?	Compound heterozygote: maternal and paternal	U
#11	<i>ABCC8</i> Exon 8	c.1254_1284dup	p.Met429X	Paternal heterozygous (focal lesion)	U

R = responsive to diazoxide, U = unresponsive to diazoxide (i.e. requiring second line treatment with Octreotide or surgery).

were recessively inherited. In those CHI patients with *KCNJ11* mutations, four were heterozygous (two paternal and two maternal) and one was homozygous. In total, three novel heterozygous *ABCC8* variants of uncertain clinical significance, A726T (c.2176G>A), A978T (c.2932G>A) and c.3870+7G>A, were each identified in a single proband and the previously reported *ABCC8* variant, c.-8G>T, was identified in two unrelated cases (17). These variants were considered unlikely to be pathogenic as all patients had inherited the variant from an unaffected parent and a second mutation had not been identified by direct sequencing. In addition, all these variants affected bases that were not conserved across species and *in silico* analysis, which included splicing prediction for c.3870+7G>A, suggested that the substitutions were unlikely to be disease causing (Alamut Interactive Biosoftware, version 1.5, Rouen, France; www.fruitfly.org).

Paternal heterozygous *K_{ATP}* channel mutations were present in 13 children (13% of cohort), of which 11 (85%) were in *ABCC8* and two were in *KCNJ11*. In two of these children, paternal heterozygosity was inferred by the absence of maternal mutations. In these children, no maternal mutation was identified on sequencing the exons and exon–intron boundaries. Maternal heterozygous *K_{ATP}* channel mutations were present in five (5%) children, three in *ABCC8* and two in *KCNJ11*. *De novo* *ABCC8* mutations, with no identified parent of origin, were present in four children. Microsatellite analysis confirmed family relationships in all cases.

Clinical outcome: subtotal pancreatectomy for non-focal CHI

In 13 children (13% of cohort) who required subtotal pancreatectomy for non-focal CHI, rapid genetic screening identified ten *ABCC8* mutations, two *KCNJ11* mutations and no mutation in one of the patients. Medical treatment was unsuccessful in

achieving euglycaemia in these cases, and subtotal pancreatectomy was carried out for suspected non-focal (diffuse) CHI (Table 2), which was subsequently confirmed by histological examination. In this group, we found that 54% (*n*=7/13) of patients were compound heterozygous or homozygous for *K_{ATP}* channel mutations and 23% (*n*=3/13) were heterozygous for a paternal *ABCC8/KCNJ11* mutation. In a further patient, paternal inheritance was inferred by the absence of the *ABCC8* mutation in the mother's sample; the sample from the father was not available for testing. In one of the patients with a novel paternal heterozygous *ABCC8* mutation (patient #7, Table 1), histology was in keeping with diffuse CHI but loss of maternal heterozygosity was noted in the pancreatic tissue, suggesting the possibility of a giant focal lesion. Pancreatic tissue was not available for loss of heterozygosity studies in the three remaining patients with paternally inherited mutations and diffuse disease. MLPA analysis was undertaken on one of the probands, where there was sufficient DNA, and normal gene dosage was observed.

Post-surgery, four children developed diabetes and needed long-term insulin treatment. Exocrine pancreatic insufficiency was noted in four individuals, and one child who developed diabetes stopped insulin injections after 1 year.

Clinical outcome: focal CHI and lesionectomy

Focal lesions were diagnosed in a total of eight children (8% of cohort) on ¹⁸F-Dopa PET–CT scan, all of whom underwent a lesionectomy (Table 2). In seven children with paternally heterozygous mutations, focal CHI was confirmed by histology and through the loss of heterozygosity (due to paternal uniparental isodisomy) in pancreatic tissue biopsies. In one child, a *de novo* mutation in *ABCC8* was observed with the presence of a

Table 2 Clinical outcomes and results of genetic testing. Outcomes included remission, stable on medical treatment, focal lesionectomy and subtotal pancreatectomy in relation to categories (no mutation identified, maternal and paternal heterozygous *K_{ATP}* channel mutations, compound heterozygous/homozygous *K_{ATP}* channel mutations, *de novo* *K_{ATP}* channel mutations and other mutations (*GCK*, *GLUD1* and *HNF4A*) identified by genetic mutation testing in children with CHI.

	Remission	Stable on medical treatment	Surgery		Total number of cases
			Focal lesionectomy	Subtotal pancreatectomy	
No mutation identified	43	22	0	1	66
Maternal heterozygous	5	0	0	0	5
Compound heterozygous/homozygous	0	3	0	7	10
Paternal heterozygous	0	2	7	4	13
<i>De novo</i> <i>K_{ATP}</i> channel mutations	1	1	1	1	4
Other mutations (<i>GLUD1</i> , <i>GCK</i> , and <i>HNF4A</i>)	0	3	0	0	3
Total number	49	31	8	13	101

solitary focal lesion in the pancreas, successfully resected by lesionectomy. In addition, four children with paternal *ABCC8* mutations who underwent subtotal pancreatectomy with histology suggestive of diffuse CHI may have had atypical forms of focal CHI. However, these children have not been included in the group with focal CHI.

The presence of paternal heterozygous mutations was more common in focal CHI than in non-focal CHI (7 (87%) vs 6 (14%), $P < 0.001$), as expected. In addition to paternal heterozygosity, we found age at presentation > 1 month to be independently associated with the diagnosis of focal CHI (odds ratio (OR) 6.1, 95% confidence intervals (1.1–35.3), logistic regression $R^2 = 0.8$, $P < 0.001$), when controlling for gender, birth weight and duration of follow up.

Clinical outcome: stable on medical treatment

Diazoxide was originally commenced in 94 of 101 patients with satisfactory response to medication observed in 64 children (68%). In 30 children who were not responsive to diazoxide (30% of cohort), s.c. octreotide injections were administered. Satisfactory glycaemic control with acceptable tolerance was achieved in four children treated with bolus subcutaneous injections of octreotide and in two children treated with continuous subcutaneous infusion of octreotide. In those stable on long-term medical treatment with either diazoxide or octreotide, 22 children (73%) carried no identifiable mutation. There were two paternal heterozygous, three homozygous/compound heterozygous and one *de novo* K_{ATP} channel mutations in the medically treated group. On medication, three children with *GLUD1/GCK/HNF4A* mutations also remained stable (Table 2).

Clinical outcome: remission

Remission was achieved in 49 children (48% of cohort) at 101 days (6 days–7.5 years) (25th, 75th percentiles 30 days, 300 days). Remission was not achieved in this cohort if children had homozygous/compound heterozygous or paternal K_{ATP} channel mutations. However, five children with maternal heterozygous *ABCC8* mutations (15% of those with K_{ATP} channel mutations) (Table 2) also underwent remission between 2 weeks and 3.8 years after diagnosis. These children had varying severity of CHI with glycaemic control achieved with diazoxide in doses between 5 and 10 mg/kg per day without the requirement for second-line treatment with octreotide or subtotal pancreatectomy.

In logistic regression ($R^2 = 0.5$, $P < 0.001$), the probability of remission was positively correlated with the absence of gene mutations (OR 16.6 (3.0–91.8), $P = 0.001$), when controlling for gender, birth weight, gestational age and follow-up duration. Remission was also more likely if either no mutations were found or

maternally inherited mutations were carried (OR 45.5 (5.6–362.0), $P < 0.001$; $R^2 = 0.5$, $P < 0.001$). A satisfactory response to diazoxide was also positively associated with the probability of remission (OR 112.8 (10.6–1196.0), $P < 0.001$; $R^2 = 0.6$, $P < 0.001$), when controlling for the same covariates.

In children who achieved remission and did not have mutations, initial glucose requirement was variable and was not different from those who remained on medication. Birth weight was not lower in this group and was not correlated with the probability of remission, when tested in logistic regression, while controlling for other factors.

Discussion

In this paper, we have reviewed the clinical outcomes in a contemporary cohort of 101 children with CHI following rapid K_{ATP} channel gene mutation analysis. In our screen, a significant proportion of children (32%) with CHI had genetic mutations identified in the *ABCC8/KCNJ11* genes, which encode for the subunits of K_{ATP} channels, SUR1 and Kir6.2. In this cohort, the frequency of novel *ABCC8/KCNJ11* mutations was relatively high (34%). In those without mutations at rapid screening, three other CHI-related gene mutations were also identified. While several papers have suggested that rapid genetic analysis of K_{ATP} channel genes has the potential to influence the clinical management strategies of patients diagnosed with CHI (1, 5, 18), there have been no detailed studies of the relationship between the profile of these mutations on clinical outcomes in a large population comprising medically responsive and unresponsive patients with CHI. In this study, we have analysed how K_{ATP} channel mutation analysis soon after diagnosis in children with CHI influenced clinical outcomes such as subtotal pancreatectomy, the need for ^{18}F -Dopa PET-CT scan to diagnose focal CHI and the achievement of long-term stability on medical treatment or remission without the need for treatment.

Failure of medical treatment leading to subtotal pancreatectomy was more likely in those patients with homozygous/compound heterozygous K_{ATP} channel mutations (70%). However, in those carrying maternal heterozygous K_{ATP} channel mutations, the probability of remission and hence avoiding the need for subtotal pancreatectomy was much higher (100%). This disagrees with the conclusions of Christesen *et al.* (18) who reported that the presence of maternal or homozygous/compound heterozygous mutations was predictive of diffuse disease requiring pancreatectomy. These differences may arise from the fact that our observations were made on a much larger cohort of patients (101 versus four patients).

Mutations in *ABCC8/KCNJ11* were found in 95% of the CHI patients requiring surgery for medically

unresponsive CHI. A similar figure, 81%, has recently been reported in a cohort of 109 diazoxide-unresponsive CHI patients (9).

In total, eight children (8% of the cohort) were found to carry focal lesions in the pancreas following ^{18}F -Dopa PET-CT scan. The determination of paternal heterozygous mutations is now recognised as a strong positive indicator of focal CHI lesions and prompts PET-CT scanning prior to focal lesionectomy in those centres where the facility is available (5, 7, 13, 18–21). In our study, all the eight patients were positive for a paternal heterozygous K_{ATP} channel mutation.

Although most non-focal or diffuse CHI have been known to occur in the neonatal period, there are no reports of the timing of presentation in those with focal CHI lesions (1, 21). We observed that children diagnosed with CHI beyond the neonatal period had a greater likelihood of a focal CHI diagnosis, with the mean age of presentation of focal CHI observed at 62 (range 1–270) days, whereas other reports, albeit anecdotal, indicate an earlier age of onset (22).

The presence of paternal heterozygous K_{ATP} channel mutations in CHI patients is not exclusively linked to focal CHI. In this study, we found that 16% of patients with this pattern of inheritance were stable on medical therapy and that 31% of patients required a subtotal pancreatectomy. In our cohort, four patients may have had atypical focal CHI but have been counted in the group with diffuse CHI who underwent subtotal pancreatectomy. Therefore, it is possible that the number of children with paternal heterozygous K_{ATP} channel mutations and having focal CHI are under-represented. Nonetheless, it is not entirely clear why some children with paternally inherited mutations do not have focal disease. However, it is important to note that similar observations were made recently by Bellanne-Chantelot *et al.* (2010) (9) in a medically unresponsive cohort of 109 patients and by Fernandez-Marmiesse *et al.* (2006) (23) who reported paternally derived mutations in five non-focal diazoxide-unresponsive CHI patients in the Spanish CHI cohort. Although *ABCC8* and *KCNJ11* are not imprinted genes, Bellanne-Chantelot *et al.* (2010) have suggested that epigenetic anomalies could account for these observations because both the genes are close to the imprinted region of 11p15.5. It is also possible that a maternal mutation was present but not identified on rapid K_{ATP} channel mutation testing in those children with non-focal CHI carrying a paternal heterozygous mutation.

We also found that a significant proportion (18%) of children who tested positive for *ABCC8/KCNJ11* mutations achieved euglycaemia with medical treatment. In this group, 10% ($n=3/31$) were heterozygous and 10% ($n=3/31$) were homozygous/compound heterozygous for K_{ATP} channel mutations. Remission was achieved in a significant proportion of the whole cohort (48%). Remission was more likely in those without identified genetic mutations. In children who

were stable on long-term medical therapy or achieved remission, 15% tested positive for K_{ATP} channel mutations and 4% of patients carried *GLUD1*, *GCK* or *HNF4A* mutations. Again, these figures compare favourably with those of other large cohorts where incidences of 17 and 6% were reported for *ACBC8/KCNJ11* and *GLUD1* mutations, respectively (6, 9, 23). Our observations, therefore, reinforce the prognostic value of rapid K_{ATP} mutation analysis at diagnosis in all children with CHI, not just in those with medically unresponsive CHI.

Transient CHI suggesting remission has recently been reported to occur in the presence of a K_{ATP} channel mutation (24), but the disorder has not been extensively reported (7, 24). In our cohort, six children (18%) of those with K_{ATP} mutations underwent remission. The causes and mechanisms of spontaneous remission in CHI are not clear. Some cases result from mutations in *HNF4A* where CHI remits during childhood, but diabetes is likely to develop during adolescence or adulthood (6, 25). In our cohort, the absence of detected K_{ATP} channel gene defects was associated with a greater likelihood of spontaneous remission. It is possible that K_{ATP} mutation-negative children with transient CHI may have gene abnormalities in pathways regulating insulin secretion but are not present in K_{ATP} channel genes or genes regulating energy metabolism (12).

The timing of remission has not been described in previous studies. In this study, we have observed that a significant proportion of children with CHI underwent remission between 1 month and 1 year. However, some children remitted beyond a year and were as late as 7.5 years old when stopping diazoxide (and chlorothiazide) with an achievement of a satisfactory glycaemic status.

Conclusions

We found that rapid screening of K_{ATP} channel genes (*ABCC8* and *KCNJ11*) was useful in the clinical management of children with CHI. In 70% of children carrying homozygous/compound heterozygous *ABCC8/KCNJ11* mutations, subtotal pancreatectomy was required for failed medical treatment of non-focal (diffuse) CHI. Those with paternal heterozygous mutations required ^{18}F -Dopa PET-CT scanning, with focal CHI amenable to focal lesionectomy being diagnosed in half of the children. All children with maternal heterozygous mutations achieved remission. In those without identified mutations, most children achieved either remission or long-term stability on medical treatment, although occasionally subtotal pancreatectomy was required. We conclude that rapid genetic analysis for all CHI patients has important implications for genetic counselling, diagnostic and prognostic aspects of CHI.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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