CONGENITAL HYPERINSULINISM DUE TO COMPOUND HETEROZYGOUS MUTATIONS IN THE *ABCC8* GENE: 20 YEARS EXPERIENCE OF A NATIONAL REFERRAL CENTRE

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Introduction

Congenital hyperinsulinism (CHI) is a complex heterogeneous condition in which insulin secretion is unregulated and inappropriate for the concentration of blood glucose. The molecular basis of CHI involves defects in key genes that control insulin secretion in the pancreatic β-cell, with the *ABCC8* and the *KCNJ11* genes being the most common affected.

Objective

To analyse the clinical presentation, genotype and response to treatment of patients diagnosed with CHI due to compound heterozygous mutations in the *ABCC8* or *KCNJ11* genes.

Methods

Retrospective review of clinical records of all patients diagnosed in our Centre with CHI due compound heterozygous mutations, between 1994 and 2015.

What is already known on this topic

- Compound heterozygous mutations in the *ABCC8* and *KCNJ11* account for approximately 13% of all CHI mutations. These mutations have been associated with diffuse disease unresponsive to diazoxide, therefore affected individuals have traditionally been treated with total or subtotal pancreatectomy.
- Clinical characterisation of some mutations has highlighted significant heterogeneity within affected patients suggesting that coexistent mutations may interact to modify both the K_{ATP} channel function and the disease severity.

What this study adds

- Although individuals affected by CHI due to compound heterozygous mutations in the *ABCC8* gene generally present with severe hypoglycaemia refractory to diazoxide, transient and diazoxide responsive CHI have also been described.
- Newer agents such as lanreotide and sirolimus represent an alternative pharmacological option that may be beneficial in conservatively treated patients with CHI.
- Clinicians should be aware of this highly variable genotype-phenotype correlation to avoid pancreatic surgery and provide appropriate genetic counseling.

Results

All patients recruited into the study (Table 1) were referred to Great Ormond Street Hospital which is a National and International referral Centre for CHI. Only patients with biochemically confirmed CHI (Table 2) caused by compound heterozygous mutations in the *ABCC8* gene were included (Tables 3 & 4, new mutations in red. Genetic analysis of both *ABCC8* and *KCNJ11* genes was performed, but only mutations of the former were found). Functional analysis of new mutations was not conducted. Our cohort of patients showed high variability regarding response to therapy (Table 5).

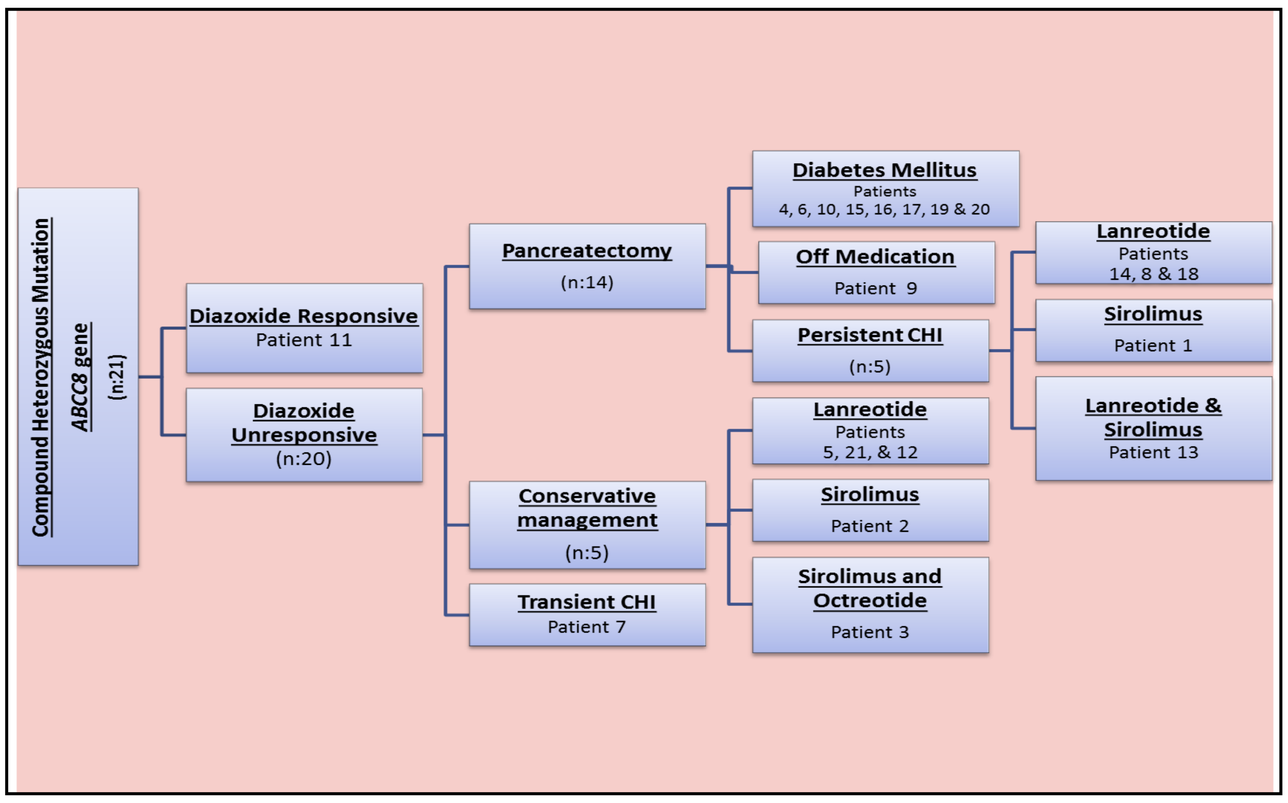
PARAMETER	TOTAL POPULATION (n:21)	
GENDER	11 Females (52.4%)	10 Males (47.6%)
ETHNICITY	18 White British (85.7%) 2 White European (9.5%) 1 Indian (4.8%)	
GESTATIONAL AGE	38 weeks	(35 – 40 weeks)
BIRTH WEIGHT	4422.9 gr (± 660.4 gr)	2.64 SD (± 1.15)
CONSANGUINITY	No - 20 patients (95.2%)	No data - 1 patient
FAMILY HISTORY OF DIABETES	No - 16 patients (76.2%) Yes - 2 patients (9.5%)	No data - 3 patients
FAMILY HISTORY OF CHI	2 families	(4 patients)
GESTATIONAL DIABETES	No - 18 patients (85.7%) Yes - 1 patient (4.8%)	No data - 2 patients
AGE AT PRESENTATION	18.13 hours (± 24.45)	(21 days – 12 months)

Table 1

LABORATORY VALUES FOR DIAGNOSIS OF CHI (n:21)	
GLUCOSE (mmol/L)	1.93 (± 0.51)
INSULIN (mU/L)	28.52 (± 22.53)
C PEPTIDE (pmol/L)	624.87 (± 397.77)
KETONE BODIES (mmol/L) (n:16)	0.05 (± 0.02)
NON ESTERIFIED FATTY ACIDS (mmol/L) (n:16)	0.20 (± 0.02)
MAXIMUM GLUCOSE INFUSION (mg/kg/min)	20.7 (± 5.23)

Table 2

Table 5



Genetic Analysis

PATIENT MALE	MATERNAL PROTEIN	MATERNAL DNA	PATERNAL PROTEIN	PATERNAL DNA
3	p.?	c.3992-9G>A	p.T1381fs	c.4141_4143delinsCA
5	p.V222M	c.664G>A	p.E515K	c.1543G>A
6	p.R1421C	c.4261C>T	p.T1532A	c.4594A>G
7	p.R168C	c.502C>T	p.S606T	c.1817G>C
8	p.[I320N;W739C]	c.[959T>A; 2217G>T]	p.?	c.1176+2T>C
12	p.R74W/	c.220C>T	p.I1436S	c.4307T>G
13	p.His36Arg(pH36R)	c.107A>G	p.?	c.2041-21G>A
15	p.G70E	c.207T>C	p.R1419H	c.4256G>A
18*	p.?	c.4311-2A>G	p.R248X	c.742C>T
20**	p.R16P	c.47G>C	p.?	c.2116+3A>G

PATIENT FEMALE	MATERNAL PROTEIN	MATERNAL DNA	PATERNAL PROTEIN	PATERNAL DNA
1	p.?	c.3992-9G>A	p.F1338del	c.4163_4165del
2	p.G316R	c.946G>A	p.?	c.3992-9G>A
4	p.?	c.1176+2T>C	p.V21D	c.62T>A
9*	p.?	c.4311-2A>G	p.R248X	c.742C>T
10	p.K242fs	c.725delA	p.R1437X	c.4309C>T
11	p.R526C	c.1576C>T	p.H627fs	c.1879delC
14	p.?	c.2041-21G>A	p.W1339X	c.4017G>A
16	p.H627fs	c.1879delC	p.M429fs	c.1254_1284dup31
17	p.R526C	c.1576C>T	p.S1483R	c.4447A>C
19**	p.R16P	c.47G>C	p.?	c.2116+3A>G
21	p.R1215W	c.3643C>T	p.G735E	c.2204G>A

Tables 3 & 4
*Note: * and ** are siblings*

Conclusions

Due to their heterogeneity in terms of clinical presentation and response to medical therapy, patients with CHI due to compound heterozygous mutations in the *ABCC8* gene require individualised assessment to achieve the best outcome.

References

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