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Syndromic Forms of Hyperinsulinaemic Hypoglycaemia – A 15-year follow-up Study

Running title: Hyperinsulinaemic Hypoglycaemia and syndromes

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Summary:

Objective: Hyperinsulinaemic hypoglycaemia (HH) is one of the commonest causes of hypoglycaemia in children. The molecular basis includes defects in pathways that regulate insulin release. Syndromic conditions like Beckwith-Wiedemann (BWS), Kabuki (KS) and Turner (TS) are known to be associated with a higher risk for HH. This systematic review of children with HH referred to a tertiary centre aims at estimating the frequency of a syndromic/multisystem condition to help address stratification of genetic analysis in infants with HH.

Methods: We performed a retrospective study of 69 patients with syndromic features and hypoglycaemia in a specialist centre from 2004 to 2018.

Results: Biochemical investigations confirmed HH in all the cases and several genetic diagnoses were established. Responsiveness to medications and the final outcome following medical treatment or surgery were studied.

Conclusions: This study highlights the association of HH with a wide spectrum of syndromic diagnoses and that children with features suggestive of HH-associated syndromes should be monitored for hypoglycaemia. If hypoglycaemia is documented, they should also be screened for possible HH. Our data indicate that most syndromic forms of HH are diazoxide-responsive and that HH resolves over time; however a significant percentage continues to require medications years after the onset of the disease. Early diagnosis of hyperinsulinism and initiation of treatment is important for preventing hypoglycaemic brain injury and intellectual disability.

Keywords: Hyperinsulininaemic hypoglycaemia, syndromes, Beckwith-Wiedemann syndrome, Kabuki syndrome, Turner syndrome.

Introduction

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Hyperinsulinaemic hypoglycaemia (HH) (MIM: 602485) is the commonest cause of persistent hypoglycaemia in infancy. It is a rare disorder, defined as inappropriate insulin secretion at the time of hypoglycaemia and presents in its more severe form in the neonatal period or in a milder form in infancy or childhood[1]. HH is a genetically and phenotypically heterogeneous disease. The underlying pathogenetic mechanism is dysregulated insulin secretion secondary to mutations in different genes that are involved in the regulation of insulin secretion from the β-cells. In up to 50% of cases a monogenic aetiology is identified. The ATP-sensitive potassium channel (K_{ATP}), encoded by *ABCC8* and *KCNJ11* genes, plays an essential role in controlling insulin exocytosis from the pancreatic β-cell. Mutations in these two genes account for the vast majority of HH cases in which a genetic cause is identified[2]. However, in the remaining 50% of HH cases, the underlying (molecular) mechanism remains unknown and epigenetic, polygenic or environmental causes have been suggested[2].

HH has been reported in syndromes, including Beckwith-Wiedemann syndrome (BWS) (MIM: 130650), Kabuki syndrome (KS) (MIM: 147920), Simpson-Golabi-Behmel syndrome (MIM: 312870), Usher-Congenital Hyperinsulinism Syndrome (in patients who have a contiguous gene deletion at 11p15 which includes ABCC8) (MIM: 276904), homozygous 11p14-15 deletion syndrome (MIM: 606528), Sotos syndrome (SS) (MIM: 117550), Costello syndrome (MIM: 218040), Trisomy 13, Perlman syndrome (MIM: 267000), Timothy syndrome (MIM: 601005), Poland syndrome (MIM: 173800) and Turner syndrome (TS), particularly mosaic X loss[3-8].
The present study reports children with syndromic features diagnosed with HH over a consecutive period of 15 years in a specialist quaternary centre. The clinical presentation and the genotype-phenotype correlation of syndromic forms of HH are described. The aim of this study was to highlight the variability in the syndromes associated with HH in terms of clinical characteristics, response to treatment and long-term outcome.

Materials and Methods:

69 children presenting with hypoglycaemia and syndromic features and diagnosed with HH over a period of 15 years, were retrospectively studied. All the patients were managed at Great Ormond Street Hospital for Children NHS Foundation Trust from 2004 to 2018.

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HH was diagnosed according to well-established criteria (5), including plasma glucose concentrations <2.7 mmol/L or <50 mg/dl, detectable insulin and elevated c-peptide at the time of hypoglycaemia, glucose requirements >6-8 mg/kg/min to maintain normoglycaemia (>3.5 mmol/L), inappropriately low non-esterified fatty acids (NEFA) and ketone body concentrations in the blood at the time of hypoglycaemia and positive glycaemic response (>1.5 mmol/L) to intramuscular or intravenous glucagon. Patient data were obtained from medical records review. A patient was deemed responsive to medical therapy if intravenous support and glucagon could be discontinued, and euglycaemia maintained on an age-appropriate enteral feeding regime with age-appropriate fasting tolerance. Complete responsiveness to diazoxide was defined as achievement of glycaemic control and age-appropriate fasting tolerance with diazoxide only, whereas partial responsiveness as achievement of glycaemic stability with concomitant use of more than one agents and feeds. The absence of glycaemic improvement despite combination of medications defined unresponsiveness. Genetic testing for clinically suspected syndromes was performed, as well as HH genetic testing for known genes in diazoxide unresponsive cases or in cases that needed a high diazoxide dose. Parental genotyping was performed when a causative variant was detected.

Genetic testing was directed by clinical phenotype and included microarray, methylation studies, targeted single gene or targeted next generation sequencing undertaken in an accredited UK diagnostic laboratory.

Results:

69 patients (37 females) who presented with hypoglycaemia were included in the study. 30% were born prematurely (gestational age: 31-37 weeks), 8% were born small for gestational age (SGA) (birth weight <-2SDS) and 41% were born large for gestational age (LGA) (birth weight >2SDS). Among the patients who were born LGA, 48.1% had BWS. The percentage of LGA in the different cohorts was 56.5% for the BWS patients (13 of the 23 patients), 44.4% for the Kabuki patients (4 of the 9 patients) and 16.7% for the TS patients (1 of the 6 patients). Two patients with KS (22.2%) and 1 patient with TS (16.7%) were born SGA. 81% of the cases presented with hypoglycaemia at birth or within the first month of life. Of the remaining patients, the majority exhibited hypoglycaemia during the first year of life, whereas the oldest age at presentation of

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hypoglycaemia was 9 years old. HH was confirmed in all the cases. One of the patients died due to multiple co-morbidities but did respond to Diazoxide.

The underlying syndromes/syndromic features related to HH are shown in Table 1, where BWS represents the biggest group (n=23), followed by KS (n=9) and TS (n=6). Two patients with syndromic features and one suspected to have CHARGE syndrome (MIM: 214800) (due to hemihypertrophy, ventricular septal defect, choanal stenosis, right pyriform aperture stenosis, rib anomalies, scoliosis, sacral agenesis and developmental delay) had further genetic testing that confirmed a diagnosis of *ABCC8*-related HH.

The clinical characteristics, genetic findings, and management of the 3 most frequently observed syndromes (BWS, KS, TS) associated with HH are shown in Tables 2-4. Responsiveness to diazoxide was found in 72.2% of BWS (13 of the 18 patients who were trialed on diazoxide), 87.5% of KS patients (7 of the 8 patients who were trialed on Diazoxide) and 100% of TS patients. Pancreatectomy was required in 13% (3/23) of BWS and 22% (2/9) of KS. The dose of diazoxide (mg/kg/day) to which response was observed (median +/- interquartile range (IQR)) was: 10 (10) for BWS, 5 (0) in KS and 8.1 (2.8) in TS. HH resolved in 74% (17/23) of BWS patients by age of 0.9 (2.2) years, 55% (5/9) of KS patients by a median+/-IQR age of 1.2 (3.5) years and 66% (4/6) of TS patients by age of 2.6 (3.2) years, respectively. The initial effective dose of diazoxide was not related to a lower rate of resolution. Specifically, approximately 73% of the patients who did not exhibit resolution of HH and 69% of the patients who exhibited resolution of HH were administered the lowest initial dose of 5 mg/kg/day of diazoxide. Furthermore, of the patients who are still on treatment for HH, the initial effective diazoxide dose ranged from 5 to 21 mg/kg/day and the later dose ranged from 10 to 15 mg/kg/day, whereas of the patients who exhibited resolution of HH, the initial dose ranged from 5 to 20 mg/kg/day and the later dose ranged from 10 to 15 mg/kg/day.

On the whole, fifty-six cases (≈88.9%) were responsive to diazoxide, at a dose ranging from 3 to 20 mg/kg/day. Chlorothiazide was given in conjunction with diazoxide in the majority of the cases, whereas in rare cases (≈2%) furosemide and spironolactone were used for stronger diuretic effect. Frequent feed boluses or continuous feeding were used as adjuvant measures for prevention of hypoglycaemia in 22% of the patients.

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Side effects were noted in one patient with BWS who developed pulmonary hypertension and in two more patients who developed fluid retention. One case was proven partially responsive to diazoxide and unresponsiveness to diazoxide was noted in 5 patients. Five cases were treated with Octreotide and two with Sirolimus.

Pancreatectomy was performed in 7 patients (5 subtotal and 2 partial pancreatectomy), 5 patients who were not responding to medical treatment (2 patients with BWS, 1 patient with KS, 1 patient with Costello and 1 patient with Usher syndrome) and 2 patients who had a suspected focal lesion (1 with BWS and 1 with KS) but continued to have HH post-pancreatectomy. The two subjects who had partial pancreatectomy (one with BWS and one with X-linked Kabuki syndrome) were partially responsive to Diazoxide and 18F-DOPA PET scan showed a possible focal lesion. Post-surgery, these two children are effectively treated with diazoxide (4-7 mg/kg/day) and able to fast age-appropriately. Four children who had subtotal pancreatectomy were euglycaemic soon after surgery, confirmed by age-appropriate fasting tolerance without medical therapy. The remaining one patient required octreotide/sirolimus and prednisolone, which was subsequently stopped.

The clinical presentation and additional features of the patients who underwent pancreatectomy are shown in Table 5.

At the last follow-up visit, HH had resolved in 41 patients (≈60%): 3 patients (4.3% of the total population) had immediate resolution of HH post subtotal pancreatectomy, 2 patients were not surgical responders, but had resolution approximately 3 and 15 years post-pancreatectomy, respectively, and 22 patients (33%) are still on treatment for HH (15 on diazoxide; 3 on octreotide; 3 on lanreotide; 1 on acarbose). None of the two patients who had partial pancreatectomy exhibited resolution of HH.

Discussion

Recurrent syndromic diagnoses

BWS is the most common syndrome causing HH with almost half of affected individuals presenting with hypoglycaemia, usually from the first day of life. Hypoglycaemia is mild and transient in the majority of the cases, but less frequently it can be severe and persistent[9]. There are

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a number of different genetic aetiologies for BWS but severe forms are associated with paternal uniparental isodisomy at 11p15 (UPD 11p15). Analysis of the methylation status at two 11p15.5 imprinting control centres (IC1 and IC2) detects the majority (80%) of BWS cases (10). Approximately 5% of children with BWS have a *CDKN1C* mutation that is not detected by methylation studies. Focal forms of HH due to pathogenic variants in K_{ATP} genes involve paternal 11pUPD and are limited to a small area of islet overgrowth. The typical 11pUPD BWS form of HH is associated with a larger area of islet adenomatosis involving half or more of the pancreas and is usually accompanied by manifestations in other organs (eg hemihypertrophy, macroglossia). There have been reports of patients with BWS and HH due to paternal UPD of chromosome 11, extending from the BWS locus at 11p15.5 to the K_{ATP} channel genes 11p15.1 unmasking an autosomal recessive mutation in *ABCC8* or *KCNJ11* within the pancreatic tissue (11, 12). Clinical features of BWS can be variable and should be considered in patients with HH with hemihypertrophy or even subtle lateralized overgrowth of a single limb/organ, without other clinical manifestations of BWS. This was also noted in our study and Tables 2a, 2b, and 2c describe in detail the genetic, clinical findings and responsiveness to treatment. In our experience, only about half of the patients with BWS responded to diazoxide, given at a moderate dose (mean dose: 10 mg/kg/day) and in the majority of those cases HH usually resolves within the first two years of life.

Kabuki syndrome is caused by pathogenic variants in lysine-specific methyltransferase 2D (MLL2, encoded by *KMT2D*) and lysine-specific demethylase 6A (*KDM6A* on Xp11.3 which escapes X inactivation). Hypoglycaemia in KS can be caused by combined pituitary hormone deficiency, isolated growth hormone deficiency or isolated adrenal insufficiency (13, 14) or due to HH, possibly as a result of epigenetic changes in causative genes (15, 16). The *KMT2D* and *KDM6A* genes are histone modifiers and, as such, they are implicated in molecular processes including methylation, acetylation, phosphorylation and ubiquitination. All these processes may have an impact on K_{ATP} channel function or pancreatic β-cell development (17). Transient hypoglycaemia has been documented to be more common than HH, albeit those with pathogenic variants in *KDM6A* seem to be at higher risk of HH (18). Our data (Table 3 highlights the clinical characteristics of patients with KS) shows that over 75% of KS patients with HH responded to diazoxide, requiring a low dose (mean dose: 5 mg/kg/day) and HH resolved within the first couple of years of life in half of our cases.

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It has been reported that infants with Turner syndrome (monosomy of the X chromosome) present with HH at a higher incidence than normal children (19), however the underlying mechanism leading to HH remains obscure. It might involve a locus on the X chromosome where anomalies may be associated with excessive insulin secretion (20). Another study suggested that haploinsufficiency for *KDM6A* (a gene implicated in Kabuki syndrome) on the X chromosome may be responsible for hyperinsulinism in Turner syndrome (19), which has also been proposed as the causative mechanism for individuals with HH and Ring X. Most of our TS patients, as shown in Table 4, responded to diazoxide, most of them at a dose of around 8 mg/kg/day, however none required pancreatectomy. Up to 66% of TS in our study HH has resolved by the age of 2.5 years.

Comparing KS, TS and BWS, patients with BWS required higher doses of diazoxide and exhibited earlier resolution of HH. A previous nationwide survey in Japan by Toda et al (21) regarding the correlation between the three syndromes (BWS, KS, SS) and HH, identified 28 cases and showed that syndromic infants with HH had shorter duration of HH than non-dysmorphic infants with transient HH.

Other rare syndromic associations with HH

Sotos syndrome is characterised by overgrowth, distinctive facial features and intellectual disability, and has been associated with transient HH in the neonatal period. It is caused by loss-of-function mutations or deletions of *NSD1*. However, one of the hypotheses proposed is that the 5q35 region may also include additional genes that could be implicated in HH (22, 23, 24). It has been reported that major anomalies are associated more frequently with 5q35 deletions compared to point mutations in *NSD1* (25). *NSD1* gene encodes a histone methyltransferase that is involved in the opening and closing of chromatin. Disrupted interaction between *NSD1* and cofactors or histones could lead to abnormal expression of insulin, or perhaps the association of *NSD1* and certain β-cell transcription factors could suppress the expression of the insulin gene (25, 26).

CHARGE syndrome, trisomy 13 and Rubinstein-Taybi syndrome (MIM: 180849) have previously been associated with HH (27-29) without a clear understanding of the underlying responsible mechanism for HH.

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It is reported that infants with Prader-Willi syndrome (MIM: 176270), may be susceptible to hypoglycaemia due to adrenal and growth hormone deficiency. However, hyperinsulinism has not been proposed as the underlying mechanism (30).

There have been case reports of single individuals with Coffin-Siris syndrome (MIM: 617808) and hypoglycaemia, but the cause of hypoglycaemia was never identified (31) and 1 patient with megalencephaly-polymicrogyria syndrome (MIM: 615938) and hypoglycaemia in whom no connection was made with inappropriate insulin secretion (32). Our team has recently reported two cases of 16p11.2 deletion syndrome and HH (33). 22q11.2 syndrome (MIM: 611867), Alagille syndrome (MIK: 118450) and trisomy 21 have not been directly associated with hypoglycaemia.

Usher syndrome is yet another syndrome that has been associated with HH (35). It is caused by mutations in *USH1C,* a gene localized next to the *ABCC8* gene on chromosome 11p15.1. A rare homozygous contiguous gene deletion including *USH1C* and *ABCC8* has been reported, causing severe HH, deafness, vestibular hypofunction, severe enteropathy and renal tubular dysfunction (34).

Hypoglycaemia is also common in Costello syndrome. HH has been reported in an individual with HRAS p.Gln22Lys mutation. A discrete pancreatic nodule, identical to a focal lesion of congenital hyperinsulinism, was identified by autopsy. However, no *KCNJ11* or *ABCC8* mutation was detected, but paternal uniparental disomy was found within the lesion, similar to the pUPD11p15.5 in Beckwith-Wiedemann syndrome (35).

In our cohort, 88.9% (56/63) of the patients were diazoxide-responsive and 60% (41/69) of the cases resolved within the first two years of life.

Of note, besides the 69 patients included in our cohort who were diagnosed with HH, we identified 8 additional patients that were diagnosed with hypoglycaemia and syndromic features, but hyperinsulinism was never confirmed (Table 6). We hypothesise that these patients with hypoglycaemia either represented transient forms of HH, that resolved before testing was performed, or idiopathic ketotic hypoglycaemia that gradually improved. Two of them had growth

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hormone deficiency causing hypoglycaemia. Diagnostic criteria for ketotic hypoglycaemia included: fasting appropriately for age and the presence of ketone levels in blood of more than 2mmol/L at the time of hypoglycaemia as well as at the end of the fast. Children that were presumed to have ketotic hypoglycaemia showed no evidence of hyperinsulinism on diagnostic fast provocation test and they only presented with hypoglycaemia at the time of illness.

In conclusion, we propose that all children with features suggestive of syndromes associated with HH must be closely monitored for hypoglycaemia and when detected be screened for possible hyperinsulinism. Conversely, the presence of additional comorbidities in patients with HH is of particular interest, highlighting the importance of a very thorough clinical assessment and a close follow-up of each individual patient with HH. Early diagnosis of hyperinsulinism and initiation of treatment is important for preventing hypoglycaemic brain injury and aggravation of the pre-existing intellectual disability in some of these syndromes. From the available treatment options, diazoxide historically represents a first line medication and our patients exhibited a high response rate to it. Further studies including prospective and long-term follow-up data are warranted in order to elucidate the possible underlying mechanisms involved in the pathogenesis of HH in each one of the associated syndromes and monitor disease progression into adulthood.

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Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Table Titles:

Table 1. Syndromes associated with HH

Table 2a. HH and Beckwith Wiedemann syndrome.

Table 2b. HH and Beckwith Wiedemann syndrome

Table 2c. HH and Beckwith Wiedemann syndrome.

Table 3. HH and Kabuki syndrome.

Table 4. HH and Turner syndrome.

Table 5: Patients who underwent pancreatic surgery for HH.

Table 6. Patients with non-hyperinsulinaemic hypoglycaemia.

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Table Legends:

Table 1. Clinical and genetic diagnosis of patients with HH.

Table 2a. Clinical features and genetic findings in patients with HH and Beckwith Wiedemann syndrome.

Table 2b. Clinical features and genetic findings in patients with HH and Beckwith Wiedemann syndrome.

Table 2c. Clinical features and genetic findings in patients with CHI and Beckwith Wiedemann syndrome.

Table 3. Clinical features and genetic findings in patients with HH and Kabuki syndrome.

Table 4. Clinical features and genetic findings in patients with HH and Turner syndrome.

Table 5. Clinical characteristics, management, outcome and comorbidities of patients who underwent pancreatectomy.

Table 6. Genetic diagnosis and clinical characteristics of 8 patients with non-hyperinsulinaemic hypoglycaemia.

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Table 1. Syndromes associated with HH

Syndrome	Number of patients		Number of patients
Beckwith Wiedemann syndrome	23	Coffin Siris syndrome	1
Kabuki syndrome	9	22q11.2 syndrome	1
Turner syndrome	6	Sotos syndrome	1
16p11.2 deletion syndrome	2	Trisomy 21	1
CHARGE syndrome	1	Trisomy 13	1
Costello Syndrome	2	45X0/XY	1
Prader-Willi Syndrome	1	Usher syndrome type 1	1
Rubinstein Taybi syndrome	2	Autosomal recessive polycystic kidney disease	1
Alagille syndrome	1	Syndromic Features (no diagnosis)	5
Megalencephaly-polymicrogyria syndrome	1	Other chromosomal anomalies (duplication/deletion)	8

Table 1. Clinical and genetic diagnoses of patients with HH

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Patient No/Sex	1/M	2/F	3/F	4/M	5/F	6/M	7/F	8/F	9/M
Genetic Report	Pat UPD11 (ratio of 1.52 to 1, 1.22 to 1 and 1.66 to 1, in favour of the paternal allele markers TH, D11S318 and D11S1984).	Pat UPD chr 11p	Pat UPD11 (ratio of 2.23 to 1 {TH} and 2.42 to 1 {D11S4177) in favour of the paternal allele).	H19 and KvDMR: normal meth; normal MS-MLPA analysis. Negative genetics for HH	KvDMR1 hypometh	H19 and KvDMR: normal meth. No mosaic pat isodisomy. No copy changes in 11p15. 80% BWS excluded*	Pat UPD11	KvDMR loss of meth	KvDMR decreased meth
Hypoglycaemia presentation, age	D 1	D 1	D 1	5 m	D 1	D 1	1st m	D 1	D 2
HH diagnosis, age	D 1	D 1	D 2	5 m	D 1	D 1	1st year	1st m	1st m
Clinical phenotype/ Comorbidities	Hemihyp, Liver cyst Raised AFP ASD, VPS, Hypertension	Hemihyp Epilepsy, LGA	Hemihyp Epilepsy, LGA	Macrog GDD Epilepsy Umbilical hernia	Macrog Epilepsy Small anterior pituitary, GHD, TSHD, LGA	Macrog Umbilical hernia	Macrog Hemihyp, LGA	Macrog Exomphalos Hemihyp, LGA	Macrog, LGA
Diazoxide Dose/range (mg/kg/d) Duration	Yes 21 From 7th d to 3 m	No Resolved 1st m. Did not require treatment	No Resolved 1st m	Yes 5-14 From 5m to 3years	Yes 5-13.2 From 12 d to 2.3 years	Yes 5 From 11 d to 10m	Yes 5-15 From 1st m to 5 years	No (spontaneously resolved)	Yes 5 From 12 d to 5 m
Diazoxide responsiveness	No	-	-	Yes	Yes	Yes	Yes, partial	-	Yes
Other HH medications or medications used to manage the side effects of diazoxide	Octreotide 20 mcg/kg/day since 14 d, Chlor (7.5 mg/kg/day)	-	-	Chlor (7.5 mg/kg/day)	Chlor (7.5 mg/kg/day)	Chlor (7.5 mg/kg/day)	Chlor (7.5 mg/kg/day) Octreotide (max 25 mcg/kg/d)	No	Chlor (7.5 mg/kg/day)
PET scan	No	No	No	No	No	No	No	No	No
Pancreatectomy Type and age Pathology	Yes, subtotal 2m	No	No	No	No	No	Yes, subtotal 2 m Atypical HH	No	No
Age at last visit	16.5 years	13.42years	12.93years	10.5 years	8.85years	2.16years	8.29 years	7.2 years	1.2 years

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Medications at last visit	Nil	Levet, Lamotrigine	Levet, Lamotrigine	Nil	GH, LT4, Levet	Nil	Melatonin	Nil	Nil
Feeds at last visit	On demand	On demand	On demand	On demand	On demand	On demand	On demand	On demand	On demand

Table 2a. Clinical features and genetic findings in patients with HH and Beckwith Wiedemann syndrome.

D: day. m: month. Pat: paternal. Meth: methylation. Hemihyp: Hemihypertrophy. Macrog: Macroglossia. ASD: atrial septal defect. VPS: valvular pulmonary stenosis. Valvular pulmonary stenosis. GHD: Growth hormone deficiency. GDD: Global developmental delay. TSHD: TSH deficiency. Chlor: Chlorothiazide. Levet: levetiracetam. LT4: Levothyroxine. GH: Growth hormone. *Genetic testing was not comprehensive and BWS was not confirmed molecularly by the genetic testing done.

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Table 2b. Clinical features and genetic findings in patients with HH and Beckwith Wiedemann syndrome.

Patient No/Sex	10/F	11/M	12/M	13/F	14/M	15/F	16/M	17/F	18/F
Genetic Report	Pat UPD11 (Increased methylation of H190DMR and decreased methylation of KvDMR imprinting control centres of chr11p15.5).	MLPA 11p15.5 normal pattern BWS 85% excluded*. Negative HH genes	KvDMR1 hypometh	KvDMR1 hypometh	Pat UPD11 (Increased methylation of H19DMR and decreased methylation of KvDMR imprinting control centres on chromosome 11p15).	11p15 H109 5' region deletion Variant found in ARID1B in child and mother, likely not to be significant	Meth and dosage analysis 11p15 normal. BWS 85% excluded*.	Pat UPD11 (Increased dosage of paternally derived alleles at both ICR1 and ICR2).	KVDMR1 hypometh
Hypoglycaemia presentation, age	D 1	D 1	D 1	D 1	D 1	D 1	D 1	D 1	D 1
HH diagnosis, age	D 1	D 1	D 1	D 16	D 1	D 1	D 1	D 1	D 1
Clinical phenotype/ Comorbidities	Macrog Hepatoblastoma, LGA	Hemihyp GDD Epilepsy Thin corpus callosum+optic chiasm	Macrog Hemihyp	Macrog Tracheomalacia Umbilical hernia, LGA	Macrog Nephromegaly Hepatosplenomegaly HIE grade 3	Protein sensitive HH Seizures Septal + right ventricular hypertrophy Macrog	ASD, PDA Splenic cyst Hemihyp, LGA	Bilateral adrenal abnormalities Liver lesions Renal pelvi-calyceal dilatation Macrog+tongue cyst, LGA	Macrog, LGA
Diazoxide Dose/range (mg/kg/d) Duration	Yes 5-10 From 7 d to 2 years	Yes 5 From 7d to 30 d	Yes 5 From 25 d to 3m	Yes 5-10 From 16 d to 2 years	Yes 5-15 From 1st m to 2.5 years	Yes 5-10 From 1st m ongoing	No Spontaneous resolution of HH before 12m	Yes 5-15 From 15d to 45d	Yes 5 From 1st m to 3 years
Diazoxide responsiveness	Yes	Yes	Yes	Yes	Yes	Yes	-	No Sirolimus responsive	Yes
Other HH medications or medications used to manage the side effects of diazoxide	Chlor (7.5 mg/kg/day)	Chlor (7.5 mg/kg/day)	Chlor (7.5 mg/kg/day)	Chlor (7.5 mg/kg/day)	Chlor (7.5 mg/kg/day)	Spironolactone+ Furosemide	No	Chlor (7.5 mg/kg/day), Octreotide 30 mcg/kg/d Sirolimus 8 mg/m^2/d	Chlor (7.5 mg/kg/day)

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PET scan	No	No	No	No	No	No	No	No	No
Pancreatectomy	No	No	No	No	No	No	No	No	No
Age at last visit	2.09 years	8.4 years	0.54 years	7.3	5.43years	0.72years	4years	3.36years	3.07years
Medications at last visit	Nil	Baclofen Valproate	Nil	Nil	Nil	Diazoxide 3.3mg/kg/d	Nil	Lanreotide 60 mg/5weekly	Nil
Feeds at last visit	On demand	On demand	On demand	On demand	On demand	On demand	On demand	On demand	On demand

HIE: hypoxic-ischemic encephalopathy**,** ASD: Atrial septal defect, PDA: Patent ductus arteriosus. D: day. M: month. Pat: paternal. Meth: methylation. Hemihyp: Hemihypertrophy. Macrog: Macroglossia. ASD: atrial septal defect. VPS: Valvular pulmonary stenosis. GHD: Growth hormone deficiency. GDD: Global developmental delay. TSHD: TSH deficiency. Chlor: Chlorothiazide. Levet: levetiracetam. LT4: Levothyroxine. GH: Growth hormone. *Genetic testing was not comprehensive and BWS was not confirmed molecularly by the genetic testing done.

*Responsiveness could not be assessed because diazoxide was not trialled at the maximum dose of 15g/kg/day.

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Table 2c. HH and Beckwith Wiedemann syndrome

Patient No/Sex	19/F	20/F	21/M	22/F	23/F
Syndrome/ Chromosomal anomaly	Negative genetics for BWS Negative HH genetics	KvDMR hypometh	Mosaic Pat UPD11	Pat UPD11 Negative HH genetics	Mosaic Pat UPD11
Hypoglycaemia presentation, age	D 1	D 1	D 1	D 1	D 1
HH diagnosis, age	D 1	D 1	4 m	D 8	D 1
Clinical phenotype/Comorbidities	Exomphalos	Tall stature Rapid weight gain	Macrog, Adrenal mass, liver lesions, Bladder polyps, Hemihyp, Neck haemangioma, Intermittent neutropenia, LGA	Macrog, PFO, Left ventricular hypertrophy, Hemihyp, Pancreatic cyst, Raised AFP, Lesions in the liver	Macrog, LGA, Bilateral nephromegaly, Hepatomegaly PFO, LGA
Diazoxide Dose/range (mg/kg/d) Duration	Yes 15 From 43 d to 68 d	No Resolved 1st m	Yes 5 From 4 m On-going	Yes 10	Yes 5-15 From 50 d to 75 d
Diazoxide responsiveness	No	-	Yes	No	No
Other HH medications or medications used to manage the side effects of diazoxide	- Chlor (7.5 mg/kg/day) -Unresponsive to Nifedipine. -Responsive to Octreotide 35mcg/kg/d (QDS sc inj) Sirolimus 2mg/m^2/d	No	Chlor (7.5 mg/kg/day)	Chlorthiazide (7.5 mg/kg/day)	Chlor (7.5 mg/kg/day), Responsive to Octreotide 30mcg/kg/d
PET scan	No	No	No	Yes Large pancreatic head cystic lesion	No
Pancreatectomy Type and age Pathology	No	No	No	Yes, partial Focal HH	No
Age at last visit	3.09 years	2.2 years	0.8 years	2.5 years	12 m
Medications at last visit	Octreotide (22mcg/kg/d, QDS sc inj)	Nil	Diazoxide (4.5mg/kg/d) Chlor (6mg/kg/d)	Diazoxide (4 mg/kg/day) Ondasetron, Esomeprazole	Octreotide 16mcg/kg/d QDS sc inj
Feeds at last visit	On demand	On demand	On demand	On bolus feeds	Daytime 4hourly Overnight continuous gastrostomy feeds

D: day. M: month. Pat: paternal. Meth: methylation. Hemihyp: Hemihypertrophy. Macrog: Macroglossia. ASD: atrial septal defect. VPS: valvular pulmonary stenosis. Valvular pulmonary stenosis. GHD: Growth hormone deficiency. GDD: Global developmental delay. TSHD: TSH deficiency. Chlor: Chlorothiazide. Levet: levetiracetam. LT4: Levothyroxine. GH: Growth hormone. QDS: 4 times per day, LGA: large for gestational age, PFO: patent foramen ovale. Inj: Injection

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Table 3. Clinical features and genetic findings in patients with HH and Kabuki syndrome.

Patient No/Sex	1/M	2/M	3/M	4/F	5/F	6/F	7/F	8/F	9/F
Genetic report	KDM6A c.3878+3A >C	KMT2D c.6595 delT	KMT2D	KMT2D c.13689C>T	KMT2D Duplication exon 11 to 14	KDM6A c.2074-2075delCA;pGln692GlyfsTer37). Negative HH genetics. Microarray: loss of ch 10q21.1 pat inherited	KMT2D mutation	Sequencing+MLPA: no mutation for KMT2D +KDM6A Negative HH genetics Microarray: normal	KDM6A c.357C>G
Hypoglycaemia	D 1	D 1	D 1	D 1	D 1	D 1	4 m	D 7	D 1
HH	D 1	D 1	D 30	D 1	D 1	D 3	4 m	D 7	D 15
Clinical phenotype/ Comorbidities	GDD Leg asymmetry Retinal dystrophy	Tetralogy Fallot Renal pelvic dilatation, LGA	GHD, GDD Diaphragmatic hernia. Cleft palate Trigonocephaly Dysplastic kidney Dysmorphic features, SGA	GDD	GDD, LGA	Facial features of KS PDA, PFO, Bilateral thelarche Abnormal clotting with low von Willebrand antigen levels /activity, LGA	Dysmorphic features Dislocated femoral head IUGR, FTT Factor IX deficiency GDD, SGA	Facial features of KS Behavioural issues Hypoglycaemic seizures Liver haematoma ASD, PFO, LGA	Dysmorphic features Failure to thrive IUGR Truncal hypotonia
Diazoxide Dose/range (mg/kg/day) Duration	Yes 5 From 25 d to 5 years	Yes 5 From 30d to 1.25years	Yes 3 From 6 m to 4.5 years	Yes 10 From 30 d to 12 m	No Spont resolution 1st m	Yes 9 From 15 d On-going	Yes 5 From 4 m On going	Yes 15	Yes 5 From 15 d On-going
Diazoxide responsiveness	Yes	Yes	Yes	Yes	-	Partial response	Yes	No	Yes
Other HH medications op medications used to manage the side effects of diazoxide	Chlor (7.5 mg/kg/day)	Chlor (7.5 mg/kg/day)	Chlor (7.5 mg/kg/day)	Chlor (7.5 mg/kg/day)	-	Chlor (7.5 mg/kg/day)	Chlor (7.5 mg/kg/day)	No	No/ Chlor (7.5 mg/kg/day)
PET scan	No	No	No	No	No	Yes (Focal head)	No	No	No

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Pancreatectomy, Tyoe and age Pathology	No	No	No	No	No	Yes, 50% Diffuse HH	No	Yes, 90% Histology unknown	No
Age last visit	5 years	11.5 years	8 years	7 years	4 m	14 m	9 m	9.5 years	2 years
Medications, last visit	Nil	Nil	GH	Nil	Nil	Diazoxide (7mg/kg/d) Chlor	Diazoxide (10mg/kg/d) Furosemide Spironolactone	Diazoxide (2.25 mg/kg/d) Chlor	Diazoxide (2.5 mg/kg/d) Chlor
Feeds at last visit	On demand	On demand	On demand	Demand daytime. OCGF	On demand	Daytime 4hourly	4 hourly oral feeds	On demand	On demand

Ch: chromosome. IUGR: Intrauterine growth retardation. GDD: Global Developmental Delay, GOR: Gastroesophageal reflux, GH: recombinant human growth hormone D: day. M: month. Pat: paternal. Meth: methylation. ASD: atrial septal defect. VPS: valvular pulmonary stenosis. PDA: Patent ductus arteriosus. PFO: Patent foramen ovale. GHD: Growth hormone deficiency. GDD: Global developmental delay. FTT: Failure to thrive. TSHD: TSH deficiency. Chlor: Chlorothiazide. Levet: levetiracetam. LT4: Levothyroxine. GH: Growth hormone. PFO: patent foramen ovale. OCGF: Overnight continuous gastrostomy feeds

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Table 4. Clinical features and genetic findings in patients with HH and Turner syndrome.

Patient No/Sex	1/F	2/F	3/F	4/F	5/F	6/F
Genetic report	45,X,15/46,X,i(X)/50	45X0	46,X,r(X)(p11q13)[22]/45,X[8]	46X, deletion (X)(p11.2)	46, X, R (X)(p11.2q13.3)24/45, X (6)Negative HH genetics	Three cell lines, the majority showing 46, Xr(X). The ring is comprised after deletion of the terminal components of the short arm of the X and long arm of the X, contains genes KDM6A, XIST and additional genes duplicated, lead to functional disomy
Hypoglycaemia presentation, age	First year of life	D 1	4 m	D 1	12 m	D 1
HH diagnosis, age	First year of life	D 1	0.4 years	D 1	12 m	D 2
Clinical phenotype/Comorbidities	GHD,Glue ears,Horseshoe-shaped kidneys,Absence seizures with Autism/ADHD	ADHDAutoimmune hypothyroidismAlopeciaRapid weight gain, LGA	GHD, EpilepsyGDD,Hydrocephalus,Spina bifida,MyelomeningoceleVit B12 deficiency	Group B streptococcal meningitis-septicaemia, cerebral necrosis, hydrocephalous, GDD, ventricular hypertrophy, Asymmetric septal defect	Absence Epilepsy, SGA	ASD, PDALeft superior vena cava, no bridging veinDiazoxide induced PH
Diazoxide Dose/range(mg/kg/d) Duration	Yes 9.3 From 1st year to 2.85 years	Yes 7 From 2 years to 11.43 years	Yes 20 From 4 m to 2.3 years	Yes 5 From 5 d, On-going	Yes 7 From 12 m, On-going	Yes 5-10 From 7d to 43 days (PH)
Diazoxide responsiveness	Yes	Yes	Yes, Partial	Yes	Yes	Yes
Other HH medications or medications used to manage the side effects of diazoxide	Chlorothiazide (7.5 mg/kg/day)	Chlorothiazide (7.5 mg/kg/day)	Chlorothiazide (7.5 mg/kg/day)	Chlorothiazide (7.5 mg/kg/day)	Chlorothiazide (7.5 mg/kg/day)	Glucagon sc infusion max 5mcg/kg/hr, Octreotide 40mcg/kg/day (in 4 daily sc inj) Changed to lanreotide 30mg /4 weeks at 7 m
PET scan	No	No	Yes, low grade uptake throughout the pancreas	No	No	YesDiffuse
Pancreatectomy	No	No	No	No	No	No

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Age at last visit	9.24 years	12.43 years	5.2 years	2.67 years	2.6 years	10 m
Medications at last visit	GH	GH, L-T4, Melatonin, Loperamide	GH, Oxybutinin, Carbamazepin, Omeprazole	Nil	Diazoxide (3mg/kg/day) Chlorothiazide	Switched to Lanreotide 30mg /4weeks (7months)
Feeds at last visit	On demand	On demand	On demand	On demand	On demand	Continuous PEG-J feeds

ASD: Atrial septal defect, PDA: Patent ductus arteriosus, PH: Pulmonar hypertension. GHD: growth hormone deficiency. GDD: Global developmental delay. ADHD: attention deficit hyperactivity disorder. D: day. M: month. GH: recombinant human growth hormone. L-T4: Levothyroxine. Vit: vitamin. Inj: injections.

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Table 5. Clinical characteristics, management, outcome and comorbidities of patients who underwent pancreatectomy.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Genetic diagnosis	Usher syndrome type 1 (homozygous deletion of Chr 11p14-15)	BWS – paternal disomy (UPD11)	BWS – paternal disomy (UPD11)	BWS – UPD11p15	Costello – *HRAS* mutation (c466T>p, Phe 156 Leu)	X-linked Kabuki syndrome - KDM6A c.2074-2075delCA; pGln692GlyfsTer37	Facial features of Kabuki syndrome – negative genetic testing (*KMT2D, KDM6A*)
Age at presentation	At birth	At birth	1st month	At birth	At birth	At birth	At birth
Gestational age	Term	Term	Term	31 weeks	Term	Term	30 weeks
Birth weight (Kg) / SDS	3.2/(-0.44)	3.72/(0,77)	5 /(3.89)	2.2/(2.19)	3.5/(-0.15)	5.1/(3.17)	2.58/(3.39)
Age of diagnosis	At birth	At birth	1 month	At birth	3 months	14 months	At birth
18F-DOPA PET/CT scan	No	No	No	Large cystic focal lesion in pancreatic head	No	Focal lesion in pancreatic head	No
Medical management at the time of diagnosis	Diazoxide	Diazoxide, octreotide	Diazoxide	-	Diazoxide	Diazoxide-Chlorthiazide	Diazoxide, octreotide
Age at surgery	19 days	2.5 months old	2.5 months	6 months old	6 months old	16 months	3 months
Pancreatectomy (resection %)/histological findings	Subtotal (70%)/ Diffuse	Subtotal (70%)/ Diffuse	Subtotal (70%)/ Diffuse	Partial (50%)/ Possibly atypical	Near-total (95%)/ Diffuse	Partial (50%)/ pancreatic head Possibly atypical	Near-total (95%)/ Diffuse
Medical management post-surgery	-	Octreotide (20 mcg/kg/day)	-	Diazoxide 5mg/kg/day	Prednisolone, lansoprazole	Diazoxide 9mg/kg/day	-
Resolution of HH	Post-surgery	16 years	Post-surgery	-	Post-surgery	-	Post-surgery
Current age	18 years	16.5 years	8.29 years	2.5	4 years	4.5 years	10.5
Current management	-	-	-	Diazoxide 4mg/kg/day	-	Diazoxide 7mg/kg/day	Diazoxide 2.25 mg/kg/d
Co-morbidities	Sensorineural deafness,	Hemihypertrophy, liver	Hemihypertrophy,	Macroglossia, patent	Hypertrophic	PDA, PFO, LVH,	ASD, PFO, liver

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	retinitis pigmentosa, gallstones, diabetes PP	cyst, ASD, mild valvular pulmonary stenosis, resolved hypertension	macroglossia requiring tongue reduction	foramen ovale, LVH, hamartoma or hepatoblastoma	cardiomyopathy, tracheomalacia, macroglossia, GORD	abnormal clotting, bilateral thelarche, cow's milk allergy, pancreatic exocrine insufficiency PP	haematoma, behavioral problems

ASD: Atrial septal defect. LVH: Left ventricular hyperplasia. PDA: Patent ductus arteriosus. PFO: Patent foramen ovale. PP: Postpancreatectomy. Sc: subcutaneous. GORD: gastroesophaegeal reflux disease

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Table 6. Genetic diagnosis and clinical characteristics of 8 patients with no confirmed hyperinsulinaemic hypoglycaemia.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Genetic diagnosis	CHARGE syndrome	Kabuki syndrome	Kabuki syndrome	600 kb of 3q22.1 and de novo del of chromosome 6	Del in chromosome 9 and de novo dup in chromosome 2	De novo chromosome 6p del and a paternally inherited chromosome 3q dup	No genetic diagnosis	16p11.2 microdel
Age at presentation	6 months	6 years	6 months	4 years	15 months		18 months	22 months
Clinical presentation	Ketotic hypoglycaemia	Hypoglycaemia during illness	Hypoglycaemia during illness	Hypoglycaemia during illness	Ketotic hypoglycaemia.	Ketotic hypoglycaemia.	Cardiorespiratory arrest during hypoglycaemia at 18 months. Hypoglycaemia during illness	Hypoglycaemic seizures at 22 months, hypoglycaemia when illness
Medical Management	Nil	Nil	Growth Hormone	Nil	Nil	Nil	Nil	Growth Hormone
Co-morbidities	Short stature, bilateral hearing impairment and bilateral vestibular hypofunction.	GDD, cleft palate, severe GORD, mild mitral stenosis and mitral regurgitation, IgA deficiency, hypothyroidism, hypertension, SLE and small scarred left kidney.	High arched palate, generalised hypotonia, skin over the dorsum of hands and feet, gross motor delay, immunodeficiency, food allergies, GHD, GORD and eczema. Small corpus callosum.	Epilepsy, GDD, short stature, small anterior pituitary gland.	Microcephaly, GDD, speech delay, central hypotonia, visual impairment.	Epilepsy, GDD, short stature.	Dyslexia, excessive body weight.	Pyloric stenosis, failure to thrive, short stature due to GHD, speech delay.

GORD: gastroesophageal reflux. Del: deletion. Dup: duplication. GDD: Global developmental delay. SLE: Systemic Lupus Erythematosus. GHD: growth hormone deficiency

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