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Case Reports

Diffuse Type Hyperinsulinaemic Hypoglycaemia of Infancy: Case Report of Management without Pancreatectomy

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Abstract Congenital hyperinsulinism is the most common cause of persistent hypoglycaemia in infancy, with neonatal onset having the worst neurological prognosis. This case describes a compound homozygous KATP channel mutation that was managed conservatively without pancreatectomy in a child with good neurological outcome.

Key words Diffuse; Hyperinsulinism; Hypoglycaemia; Infant; Pancreatectomy

Case Report

A Chinese male firstborn infant was vaginally delivered at 36 weeks 6 days gestation with birth weight of 4.18 kg. There was no maternal history of gestational diabetes and the newborn examination showed macrosomia, but no facial dysmorphism or organomegaly. Blood glucose monitoring revealed persistent asymptomatic hypoglycaemia despite formula feeding and intravenous glucose. Although the glucose infusion rate (GIR) was increased to 16 mg/kg/min via a central line, the blood glucose level (BGL) was only 1.2 mmol/L, and the corresponding insulin level was inappropriately high at 119 μIU/L (reference range 2.6-24.9 microIU/ml). Serum metabolic screening of blood gases, ammonia, lactate, cortisol, thyroxin, urinary ketones and urine organic acids were unremarkable. Diagnosis of congenital hyperinsulinism was made and the intravenous dextrose supplement was titrated against the BGL.

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A GIR of 16.4 mg/kg/minute was required to maintain the BGL over 4 mmol/L. Milk formula feeding did not induce or improve hypoglycaemia. Diazoxide was started on day one and hydrochlorothiazide was added on day 4. At diazoxide 20 mg/kg/day and hydrochlorothiazide 2 mg/kg/day, the lowest achieved GIR was still 13 mg/kg/minute. Further hypoglycaemic episodes occurred necessitating an increased GIR up to 25 mg/kg/minute. Additionally, the insulin level remained high at 43.1 μIU/L, so intravenous octreotide was started on day 5. With octreotide totaling 15 mcg/kg/day at day 8, the serum insulin level was 39.4 μIU/L but the GIR remained high at 18 mg/kg/minute. Attempts to reduce the intravenous dextrose resulted in asymptomatic hypoglycaemia (range 2.1-2.4 mmol/L) despite oral feeding with a high carbohydrate preterm formula. Nifedipine was then added on day 12 and gradually increased together with the octreotide infusion to maximum recommended doses. By one month, treatment consisted of diazoxide 20 mg/kg/day, octreotide 40 mcg/kg/day and nifedipine 2.5 mg/kg/day. Serum insulin levels ranged between 12.8-18.6 μIU/L (lowest 7.8 μIU/L) and an average GIR of 20 mg/kg/minute was able to maintain normoglycaemia.

Genetic testing focusing on functional abnormalities of the pancreatic beta cell was undertaken. Both *ABCC8* and *KCNJ11* genes were screened for mutations and a heterozygous c.815delC frame shift mutation of *ABCC8* (SUR1) was detected in both the infant and mother. Suspecting diffuse KATP hyperinsulinism, diazoxide was stopped after knowing the genetic result. With

hypoglycaemia controlled, plan was to optimise medical treatment and prevent pancreatectomy.

Stable serum insulin levels permitted administration of subcutaneous octreotide Q8H by 3 months of life and without weight dosage adjustments. Upon discharge at 4 months, octreotide dosage was 28 mcg/kg/day. High carbohydrate milk feeds were given 3-hourly with home glucose monitoring. A weaning diet of rice porridge was introduced after six months of age. Home glucose measurements were maintained 3-5 mmol/L. Polycal was replaced with starch in the milk formula after 12 months old and given 4-hourly with rice porridge thrice daily. Octreotide was changed to Q12H injections (22 mcg/kg/day).

Glucose profiling in hospital at 24 months revealed suboptimal pre-meal sugar levels and extra cornstarch per meal was added. Octreotide tachyphylaxis was also suspected with no improvement in BGL after injection. At 25 months, daytime octreotide was weaned off with C-peptide levels reassuringly stable at 0.64 nmol/L (normal range 0.27-1.27 nmol/L).

Despite having no daytime hypoglycaemias, nocturnal values were borderline due to feeding difficulties. The parents consented to a gastrostomy at 31 months and improved feeding via gastrostomy allowed nighttime octreotide to be stopped and home pre-meal glucose measurement were stable (5-8 mmol/L). Increasing the midnight gastrostomy feed permitted stopping the 3am feed with no hypoglycaemia despite fasting till 6am the next morning.

At 33 months, repeat DNA sequencing from the patient's original blood sample revealed a second paternally inherited mutation at c.2256-2475del (deletion of exons 18-21 of *ABCC8* gene). Thus, a compound heterozygous *ABCC8* SUR1 mutation now confirms diffuse KATP disease.

The child is currently 5 years old with a C-peptide level of 0.42 nmol/L. Growth and head circumference is normal with no evidence of neurological impairment or developmental delay.

Discussion

Congenital hyperinsulinism is commonly associated with psychomotor retardation, seizures, and diverse neurologic sequelae.[1,2] Despite advances in understanding pathogenesis, pre-natal genetics and surgical methods, disease management is difficult and is reflected by little change on the incidence of such mental handicaps in affected children over past decades.[1]

Congenital HI is caused by mutations in genes that regulate pancreatic β-cell insulin secretion. Glucose-induced insulin secretion is regulated in part by β-cell KATP channels. These protein channels are composed of an inwardly rectifying potassium subunit (Kir6.2) and the sulfonylurea receptor 1 (SUR1) which are encoded by genes located on chromosome 11p15.1. Changes in plasma glucose concentration results in an increase in the intracellular ATP:ADP ratio causing closure of the KATP channel and membrane depolarisation. Resultant opening of voltage gated calcium channels leads to intracellular calcium influx and insulin exocytosis. KATP channel alterations caused by mutations of the *ABCC8* (ATP-binding cassette, sub-family C, member 8) gene encoding SUR1 and of the *KCNJ11* (potassium inwardly rectifying channel, sub-family J, member 11) gene encoding Kir6.2, are responsible for the common forms of congenital HI.[1]

The genetic process in diffuse KATP disease is a homozygous or autosomal dominant mutation affecting all the beta cells throughout the pancreas.[1,3] The focal form occurs via a two-hit mechanism on the chromosome 11p5.1-15.5 region that includes loss of heterozygosity for the maternally imprinted growth-suppressor genes and reduction to homozygosity of a paternally-derived KATP channel mutation. With loss of maternal imprinting, unregulated function of the paternally imprinted insulin-like growth factor II genes results in focal hyperproliferation of the beta-cells carrying the channel mutation, whereas the rest of the pancreas has normal histology.[2,3]

This case report describes a typical presentation of KATP HI, characterised by macrosomia and persistent neonatal hypoglycaemia associated with high GIR requirements and diazoxide resistance. As focal and diffuse KATP HI are clinically undistinguishable, genetic screening for *ABCC8* and *KCNJ11* gene related mutations would aid in early diagnosis and allow appropriate genetic counselling. Nonetheless, genetic abnormalities may not be defined in over 50% of affected patients.[1]

Fortunately, a SUR1 (*ABCC8*) heterozygous frame shift mutation (c.815delC) mutation was detected in both our patient and the mother on initial genetic analyses. Focal disease was deemed unlikely and best efforts at conservative medical management was undertaken to avoid sub-total pancreatectomy. Further genetic analysis of the father's DNA later detected another heterozygous mutation (c.2256-2475del), and diffuse KATP disease was confirmed as a compound heterozygous *ABCC8* mutation.

First line management in congenital hyperinsulinism is

to avoid hypoglycaemia. Typically, patients have high glucose requirements which are titrated via a combination of high carbohydrate feeds and intravenous glucose. Recommended initial pharmacological treatment for congenital hyperinsulinsm are oral medications (Table 1) such as nifedipine, diazoxide, and hydrochlorothiazide, with intramuscular glucagon for emergency treatment of persistent hypoglycaemia.[1,2] Experience is limited and conflicting in the literature regarding the use of nifedipine and hydrochlorothiazide in HI. Diazoxide is ineffective in patients with loss of channel function mutations in *ABCC8* and *KCJ11* genes. Stabilisation of blood glucose concentration should occur within a few days in patients responsive to diazoxide.[1] Figure 1 illustrates a management flow chart for conservative management of congenital hyperinsulism due to KATP channel mutations.[4]

We propose that octreotide can be considered promptly, as soon as diazoxide is deemed ineffective to control hypoglycaemia. Octreotide can be given at up to 40 mcg/kg/day (unlabeled use in congenital hyperinsulinism), administered via subcutaneous injections or continuously by a portable subcutaneous infusion pump.[5] Octreotide is the mainstay of treatment for diffuse KATP HI disease and theoretical long-term side effects include cholelithiasis, as well as physical retardation caused by growth hormone suppression.[1,6] Literature reports of octreotide affecting linear growth in infancy, however, are inconclusive.[6] Nevertheless, tachyphylaxis and gastrointestinal side effects including steatorrhoea, reflux and abdominal bloating limit octreotide's long-term usefulness.[6,7] Drug tolerance is possible, but we never found it necessary to adjust the total daily octreotide dose per kilogram as our patient grew, and this passive weaning was a technique commonly employed by other clinicians.[7]

Milder variants of congenital hyperinsulinism exist which do not require aggressive surgical treatment.[8] These variants may be the result of exon-skipping during transcription, yielding a channel protein with missing internal amino acids but capable of partial channel function.[9] Efforts to maximise medical management must be made and await spontaneous remission. Late clinical remission on conservative therapy occurs in 40-63% of cases usually between 2 and 11 years of age.[6-8] Mechanisms for remission may be explained by gradual

Table 1 Drug table for pharmacological management of congenital hyperinsulism due to KATP channel mutations[1]

Drug	Dose	Mechanism of action	Side effects
Diazoxide	5-20 mg/kg/day in three divided doses PO	KATP channel agonist and increases gluconeogenesis	Fluid retention, hyperuricaemia, hypotension Hypertrichosis / facial coarsening, rarely blood effects (leucopenia, eosinophillia, thrombocytopenia)
Octreotide	5-40 mcg/kg/day via IV or SC infusion, or divided six to eight hourly via SC injections	Inhibits insulin release by several mechanisms: activates G protein coupled rectifier K channel; activates somatostatin receptor-5; inhibits calcium mobilisation and acetylcholine activity	Endocrine suppression (GH, TSH, ACTH), GI disturbance (cholelithiasis, abdominal bloating, nausea, anorexia, flatulence, steatorrhoea), prone to tachyphylaxis
Nifidipine	0.25-2.5 mg/kg/day in three divided doses PO	Calcium channel antagonist to inhibit insulin release	Hypotension
Chlorothiazide (used in conjunction with diazoxide)	7-10 mg/kg/day in two divided doses PO	Synergistically with diazoxide by activating non-KATP channels	Hyponatraemia; hypokalaemia
Glucagon	1-20 mcg/kg/hour IV infusion 0.5-1 mg IMI for emergency treatment of hypoglycaemia	G-protein-coupled-receptor agonist activating adenylate cyclase to increase gluconeogenesis / glycogenolysis	GI disturbance (nausea, vomiting, decreases gastric / pancreatic secretions), endocrine disturbance (increase GH concentrations, at high doses, paradoxical insulin secretion), skin rash, increases myocardial contractility

GH=Growth Hormone; TSH=Thyroid Stimulating Hormone; ACTH=Adrenocorticotropic Hormone; GI=Gastrointestinal

apoptosis of affected beta-cells.[1]

Glaser et al reported 8 patients with persistent hyperinsulinaemic hypoglycaemia of infancy who were treated with octreotide without pancreatectomy.[7] Most of the literature recommend early subtotal pancreatectomy if medical treatment is ineffective. However, in those cases medical treatment may not have been adequate and pancreatectomy may have been performed too early.[8] Pancreatectomy may be avoided in up to 50% of the patients with use of octreotide.[10] Aggressive titration of medications is paramount to rapidly control hypoglycaemic episodes and delay invasive surgery whilst waiting for hyperinsulinism workup and genetic results.

Children with hyperinsulinism managed conservatively

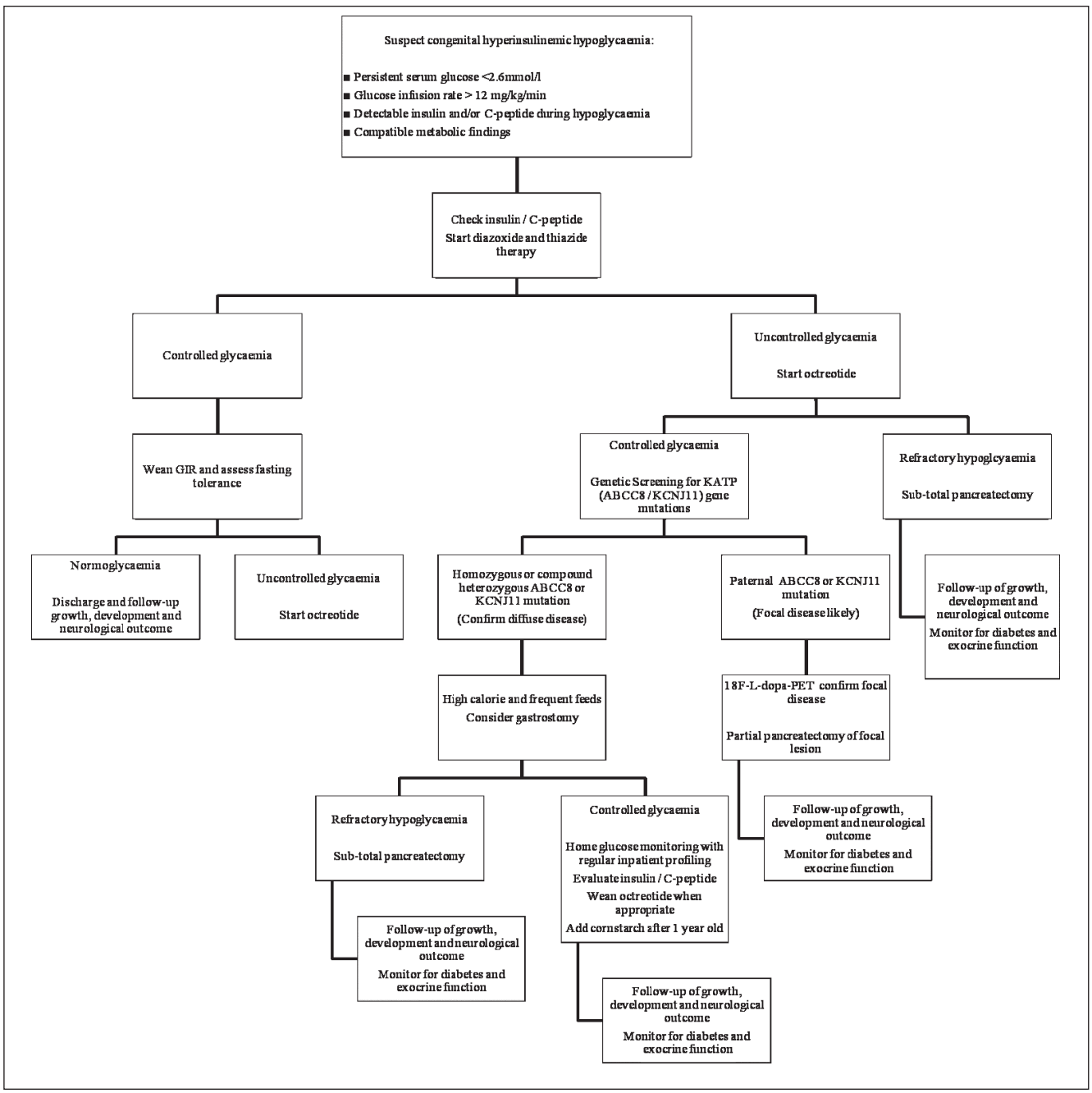

Figure 1 Basic management flow chart for conservative management of congenital hyperinsulism due to KATP channel mutations. (Adapted with modifications from Hussain K. Diagnosis and management of hyperinsulinaemic hypoglycaemia of infancy. Horm Res 2008;69:2-13)[4]

on long term octreotide therapy require regular 3-4 hourly feedings to avoid hypoglycaemia. Percutaneous gastrostomy can ensure adequate intake without force feeding. This also solves feeding problems for infants who are averse to the taste of frequent high glucose feeds and suffering from the gastrointestinal side effects of high octreotide doses. Longer fasting is tolerated with addition of raw cornstarch after the age of 1 year, permitting school and undisturbed nighttime sleep. Careful long-term monitoring is still needed with regular home BGL monitoring and periodic measurements of insulin secretion.[7] As insulin release is pulsatile, overall production is best reflected by measurement of C-peptide.[1,2]

Aggressive titration of medication and avoiding hypoglycaemia is of paramount importance, but subtotal pancreatectomy still plays an important role for those patients who do not respond to medical treatment.

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Declaration of Interest

The authors have no conflicts of interests to declare.

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