CASE REPORT

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Diazoxide-unresponsive Hyperinsulinemic Hypoglycaemia in a Preterm Infant with Heterozygous Insulin Receptor Gene Mutation

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What is already known on this topic?

Homozygous or compound heterozygous mutations in *INSR* gene cause severe insulin resistance syndromes, such as Donohue syndrome (also known as leprechaunism) and Rabson-Mendenhall syndrome, whereas heterozygous *INSR* gene mutations result in a milder phenotype, known as type A insulin resistance syndrome (type A-IR). Adults with type A-IR commonly demonstrate abnormal glucose homeostasis with fasting and postload hyperglycaemia, as well as high testosterone levels compared to age-matched controls. Phenotypes and clinical course in children, especially infants, with heterozygous *INSR* gene mutations have been reported infrequently and there is little evidence for optimal management of these infants.

What this study adds?

We report a preterm infant who presented with diazoxide-unresponsive hyperinsulinemic hypoglycaemia. Whole-exome sequencing identified a heterozygous *INSR* variant in the infant and her father. We postulate that use of diazoxide exacerbated post-prandial glucose excursion by inhibiting insulin release, while subsequent hypoglycaemia may be explained by reduced degradation or clearance of insulin due to the underlying mutation. This case highlights that in situation where mutations could not be identified by targeted sequencing of *ABCC8/KCNJ11* or *GCK* genes in an infant with suboptimal response to diazoxide, sequencing of the *INSR* gene should be considered. It is proposed that the *INSR* gene should be included in a targeted gene panel for workup of hyperinsulinism.

Abstract

Homozygous or compound heterozygous mutations in insulin receptor gene (*INSR*) lead to marked insulin resistance and hyperglycaemia in Donohue syndrome and Rabson-Mendenhall syndrome, conditions which are associated with significant morbidity early in life. In contrast, heterozygous INSR variants result in a milder phenotype, known as type A insulin resistance syndrome. While presentation in adults with this condition is well reported, phenotypes in infant are less well-characterized. Herein, we report an infant presenting with hyperinsulinemic hypoglycaemia who did not respond to diazoxide therapy. She was subsequently found to have a heterozygous *INSR* gene mutation. The patient was a female infant born at 29 weeks of gestation who developed recurrent hypoglycaemia in early infancy. Workup showed hyperinsulinism and she was started on first-line therapy with diazoxide and high-calorie feeds. However, continuous blood glucose monitoring showed post-prandial hyperglycaemia followed by rapid fall to hypogylcaemia. Whole exome sequencing was performed to investigate for diazoxide-unresponsive hyperinsulinism, which revealed a likely pathogenic mutation in the *INSR* gene, c.1246C>T p. (R416X). This nonsense mutation was inherited from the father. With the molecular diagnosis, diazoxide was stopped and she followed a diet with low glycaemic-index food. Subsequent monitoring showed stable glucose profile. This case highlights the importance of considering type A insulin resistance syndrome when no mutation is found in the *ABCC8/KCNJ11* genes in diazoxide-unresponsive hyperinsulinism. With autosomal dominant inheritance, cascade screening should be performed in family members to identify those harbouring the mutation as they are at risk of early onset diabetes.

Keywords: Hyperinsulinism, hypoglycaemia, insulin receptor

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Introduction

Mutations in the insulin receptor (*INSR*) gene are known to cause insulin resistance and hyperinsulinemia. Homozygous or compound heterozygous mutations in *INSR* gene cause the severe insulin resistance syndromes, Donohue syndrome (DS, also known as leprechaunism) and Rabson-Mendenhall syndrome (RMS), whereas heterozygous *INSR* gene mutations result in a milder phenotype, known as type A insulin resistance syndrome (type A-IR). In both DS and RMS, patients have marked hyperinsulinemia with fluctuating blood glucose levels, impaired muscle and adipose tissue development, growth failure, characteristic facial features and intellectual disability. Significant hyperglycaemia ensues when β-cells decompensate. Patients with DS, the most severe insulin resistance syndrome, seldom survive beyond infancy whereas patients with RMS can survive into early adulthood and usually die of diabetic ketoacidosis or advanced microvascular complications in the second decade of life (1). In contrast, patients with type A-IR live beyond middle age and usually present with hypoglycaemic symptoms, hypertrichosis, acanthosis nigricans and hyperandrogenism in the absence of obesity or lipoatrophy. Biochemically, these adults commonly demonstrate abnormal glucose homeostasis with fasting and postload hyperglycaemia, as well as high testosterone levels compared to age-matched controls (2).

Phenotypes and clinical course in children, especially infants, with heterozygous *INSR* gene mutations are less commonly reported. There is also a lack of evidence on how these infants can be best managed. Herein, we report a preterm infant who presented with diazoxide-unresponsive hyperinsulinemic hypoglycaemia. Whole-exome sequencing identified a heterozygous *INSR* gene mutation in the infant and her father, which helped to guide further investigation and management.

Case Report

Our proband was a Chinese female infant, born at 29 weeks of gestation for threatened preterm labour, weighing 1 kg (25th centile) and measuring 37 cm (25th centile) in length. Antenatal history was unremarkable with no gestational diabetes in the mother and there was no family history of endocrine disorders. There was no birth asphyxia and her neonatal course was relatively smooth with mild respiratory distress syndrome requiring one day of invasive ventilation, feeding intolerance and grade 1 intraventricular haemorrhage. Newborn screening for inborn errors of metabolism was normal. Parenteral nutrition was given according to standard protocol and enteral feeding was gradually stepped up.

She presented with recurrent hypoglycaemia from 1 month of life when full enteral feeding was established. Investigations showed repeated pre-feed hyperinsulinemic hypoglycemia with low serum levels of free fatty acids and ketones (Table 1).

Thyroid function, growth hormone, cortisol and ammonia levels were normal and lactate was not elevated. After cardiac assessment, diazoxide 15 mg/kg/day and hydrochlorothiazide were commenced for neonatal hyperinsulinism. Glucose polymer (Polycal) was added to feeds. However, her glucose profile worsened with more frequent episodes of pre-feed hypoglycemia. The baby was then put onto a continuous glucose monitoring system (CGMS) which revealed frequent post-prandial hyperglycaemia, ranging from 178.2 mg/dL to 309.6 mg/dL, followed by a rapid fall to the hypogylcaemic range with a nadir of 37.8 mg/dL. Insulin was still detectable (26.9-69.0 pmol/L) during these episodes of hypoglycaemia. Bolus feeding was thus halted and she was commenced on continuous milk feeding with dextrose infusion. To further investigate for diazoxide-unresponsive hyperinsulinism, genetic analysis was performed for the infant and her parents. Whole exome sequencing revealed a likely pathogenic mutation c.1246C>T p. (R416X) in exon 5 of the *INSR* gene, which resulted in a change of codon 416 from arginine to a premature termination. This nonsense mutation resulted in a truncated protein product. Her father carried the same mutation.

With the molecular diagnosis, diazoxide and Polycal supplement were gradually tapered. Dextrose infusion was weaned and bolus feeding was re-introduced on a three-hourly basis. Less post-prandial excursion, followed by a less severe plunge in blood glucose level, was observed. She finally passed an 8-hour fasting challenge with a blood glucose of 82.7 mg/dL at the end of the test and was discharged with bolus feeding at 4 months old. Regular home blood glucose monitoring showed no hypoglycaemia and she adopted a weaning diet with low glycaemic-index food. Subsequent assessment at 20 months old showed normal neurological development.

Table 1. Biochemical parameters during hypoglycaemia

	Day 37 of life	Day 82 of life
Insulin (pmol/L)	104.2	50.7
Blood glucose (mg/dL)	25.0	43.2
FFA (mEq/L)	0.11	0.13
β-OHB (mmol/L)	0.05	0.1

FFA: free fatty acid, β-OHB: beta-hydroxybutyrate

We also evaluated our proband's father in view of the mutation identified. In retrospect, he reported dizziness and tiredness after large carbohydrate meals but had never required medical attention. Physical examination showed a BMI of 26.6 kg/m^2 with no acanthosis nigricans. His fasting blood glucose, hemoglobin A1c, lipid profile and liver function tests were normal. His homeostatic model assessment for IR (HOMA-IR) was 3.0 which was $>95^{th}$ centile cut-off for normal glucose tolerance in southern Chinese (3). A 6-hour oral glucose tolerance test (OGTT) with 75 grams oral anhydrous glucose solution was performed (Table 2). He had normal glucose tolerance, but fasting hyperinsulinemia and elevated insulin-to-C-peptide ratio of 0.42 (normal range for fasting <0.1) (4). At 210 minutes, he developed asymptomatic hypoglycaemia with blood glucose of 46.8 mg/dL when paired insulin was 132 pmol/L. He was subsequently referred to the adult endocrine unit for follow up.

The parents of this infant, and the father himself, gave written consent to the writing of this manuscript. The study has been approved by the Ethics Committee of the Hong Kong West Cluster Clinical Research Ethics Review Board (HKWC-2022-249).

Discussion

We report an infant with heterozygous mutation in the *INSR* gene who presented with hyperinsulinism in the neonatal period, highlighting the need to consider this entity, especially in the setting of excessive post-prandial glucose excursion followed by reactive hypoglycaemia. Apart from the implications for treatment, cascade screening for family members is also important for the early identification of individuals at risk of young-onset glucose intolerance and insulin-resistant diabetes. These mutation carriers may benefit from dietary modification and use of insulin-sensitizing drugs, such as metformin and glitazones (2,5).

Hypoglycaemia associated with heterozygous *INSR* mutations has been described in a few adult studies (4,6,7,8). Most patients experienced hypoglycaemic during fasting and more characteristically, after a meal, which was similar to the presented case. Diagnosis in these adult studies was made with fasting hyperinsulinism, elevated fasting insulin to C-peptide ratio and hypoglycemia on prolonged OGTT. Further hyperinsulinemic-euglycaemic clamp studies showed markedly reduced insulin sensitivity and lowered metabolic clearance rate for insulin compared to controls. As a result, there is excessive insulin secretion after meal loading, which persists at high concentrations even with a falling blood glucose level, resulting in suppressed hepatic glucose output and postprandial hypoglycaemia (4,6). This phenomenon was also observed in our proband's father who demonstrated fasting and postload hyperinsulinemia, as well as hyperinsulinemic hypoglycemia (concurrent blood glucose of 46.8 mg/dL mmol/L and insulin 132 pmol/L) at 210 minutes of OGTT. Notably, he also exhibited elevated insulin to C-peptide ratio. In normal physiological conditions, insulin and C-peptide are co-secreted by the pancreas, with insulin rapidly metabolized by the liver and C-peptide slowly eliminated by the kidneys (9). Hence, elevated insulin to C-peptide ratio was suggestive of decreased clearance of endogenous insulin as a result of the underlying *INSR* mutation. While he has not developed frank diabetes, long term follow up of his metabolic profile will be necessary and avoidance of high glycaemic index food may help to ameliorate symptoms of post-prandial hypoglycaemia.

The *INSR* gene, located on chromosome 19, consists of 22 exons and 21 introns. Exons 1-11 (and part of exon 12) encode the extracellular α-subunits of the receptor that bind insulin, whereas exons 12-22 encode the β-subunits that span the plasma membrane and have an intracellular tyrosine kinase domain. Mutations in the α-subunits lead to decrease in the number of mature INSR or defective insulin binding, while mutations in the β-subunits impair autophosphorylation and subsequent activation of downstream signaling transduction. Longo et al. (10) demonstrated that mutations markedly impairing insulin binding resulted in the most severe phenotype with early demise, while mutations leaving residual insulin binding activity were associated with longer survival. However, while there is no definite genotype-phenotype correlation due to the rarity of these syndromes, mutations affecting the α-subunit of the receptor are generally associated with a more severe phenotype than those affecting the β-subunit

Table 2. Extended 6-hour OGTT of proband's father

Time (min)	0	30	60	90	120	150	180	210	240	270	300	330	360
Glucose (mg/dL)	72.0	180.0	144.0	118.8	104.4	122.4	75.6	46.8	66.6	75.6	81.0	82.8	88.2
C-peptide (pmol/L)	280	2500	2020	1920	1630	1520	830	420	310	280	210	230	280
Insulin (pmol/L)	118	1750	1229	1236	819	854	305	132	97	97	76	90	118
Insulin-to C-peptide ratio	0.42	0.70	0.61	0.64	0.50	0.56	0.37	0.31	0.31	0.35	0.36	0.39	0.42

OGTT: oral glucose tolerance test

(10,11). Hence, the majority of patients with DS have mutations in the α-subunit, while type A-IR syndrome is more frequently associated with mutations in the tyrosine kinase domain of the β-subunit (4,6,7,8,11). The nonsense mutation c.1246C>T identified in our proband and his father is located in the second leucine-rich repeat domain (L2) of the extracellular ligand-binding α-subunit. This variant was previously reported in a boy diagnosed with DS at 1 month old. Interestingly, this boy only carried a single mutation, as did our proband, but presented early with severe phenotype (12). Unfortunately, we were not able to perform functional analysis which could possibly explain the milder phenotype in our case. Nevertheless, this is the first report of a heterozygous α-subunit mutation causing neonatal hyperinsulinism with a mild presentation.

Neonatal hyperinsulinimic hypoglycaemia linked to heterozygous *INSR* mutation was first reported in four infants from three families by Sethi et al. (13). All these infants had mutations located in exon 20 of the *INSR* gene, which encode the β-subunit of the receptor. They were all born small for gestational age and developed hypoglycaemia on the first day of life. In contrast to our proband, they showed good response to diazoxide therapy (at a dose between 3-7.5 mg/kg/day) and were able to wean off the medication before 1 year of age. Diazoxide acts to open pancreatic β-cell ATP-sensitive potassium (K_{ATP}) channels and inhibit insulin secretion. The mechanism in which hyperinsulinism in these infants responds to diazoxide is not clear. In contrast to the reported cases, the glucose profile in our infant worsened after diazoxide. We postulate that use of diazoxide exacerbated post-prandial glucose excursion by inhibiting insulin release while the hypoglycaemia that follows could be explained by reduced degradation or clearance of insulin due to the underlying mutation.

The most common form of monogenic hyperinsulinism is caused by inactivating mutations in the *ABCC8* or *KCNJ11* genes, which encode subunits of the K_{ATP} channel. These mutations also account for almost 90% of diazoxide-unresponsive hyperinsulinism cases, followed by activating mutations of the glucokinase (*GCK*) gene (14,15). In contrast to infants with *INSR* mutation, those who harbour *ABCC8* or *KCNJ11* mutations typically present with fasting hypoglycaemia rather than post-prandial hypoglycaemia. In addition, post-prandial hyperglycaemia, a prominent feature in patients harbouring *INSR* gene mutations, helps to differentiate these conditions. Birth weight also provides another important clue to help identify patients with diazoxide-unresponsive hyperinsulinism due to K_{ATP} channel mutations, as these babies are usually born macrosomic. Therefore, careful history taking and biochemical phenotyping in the evaluation of hyperinsulinism are very helpful in recognizing patients with possible *INSR* gene mutations. CGMS was used to monitor the glucose profile in our proband. While accuracy might be an issue in young infant, CGMS offers great value in the evaluation of glucose fluctuation, thereby helping clinicians consider the diagnosis of *INSR* gene mutations.

Conclusion

In conclusion, the present case report details the clinical and biochemical features of an infant with hyperinsulinimic hypoglycaemia caused by heterozygous *INSR* gene mutation. Response to diazoxide therapy was poor and resulted in even more severe post-prandial hyperglycaemia. While further accumulation of clinical experience in managing this group of pediatric patients is required, accurate genetic diagnosis of the condition is essential to ensure regular monitoring of metabolic control and prompt initiation of intervention when necessary.

Ethics

Informed Consent: The parents of this infant, and the father himself, gave written consent to the writing of this manuscript.

Presented in: Abstract of this case report has been presented in the 12th Biennial Scientific Meeting of the Asia Pacific Paediatric Endocrine Society.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Sarah Wing-Yiu Poon, Brian Hon-Yin Chung, Mabel Siu-Chun Wong, Anita Man-Ching Tsang, Concept: Anita Man-Ching Tsang, Design: Sarah Wing-Yiu Poon, Data Collection or Processing: Sarah Wing-Yiu Poon, Brian Hon-Yin Chung, Anita Man-Ching Tsang, Analysis or Interpretation: Brian Hon-Yin Chung, Mabel Siu-Chun Wong, Literature Search: Sarah Wing-Yiu Poon, Brian Hon-Yin Chung, Anita Man-Ching Tsang, Writing: Sarah Wing-Yiu Poon, Brian Hon-Yin Chung, Anita Man-Ching Tsang.

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