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case report

Heterozygous Insulin Receptor (*INSR*) Mutation associated with Neonatal Hyperinsulinemic Hypoglycaemia and Familial Diabetes Mellitus: Case Series

Sethi A et al. *INSR* mutation and Neonatal Hyperinsulinemic Hypoglycaemia

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Abstract

Mutations in the insulin receptor (*INSR*) gene are associated with insulin resistance and hyperglycaemia. Various autosomal dominant heterozygous *INSR* mutations leading to hyperinsulinemic hypoglycaemia (HH) have been described in the adults and children (more than 3 years of age) but not in the neonatal period. **Family 1:** A small for gestational age (SGA) child born to a mother with gestational diabetes presented with persistent hypoglycaemia, was diagnosed with HH and responded well to diazoxide treatment. Diazoxide was gradually weaned and discontinued by 8 months of age. Later, the younger sibling had a similar course of illness. On genetic analysis a heterozygous *INSR* missense variant p.(Met1180Lys) was found in the siblings, mother and grandfather but not in the father. **Family 2:** A twin preterm and SGA baby presented with persistent hypoglycaemia, which was confirmed as HH. He responded to diazoxide, which was subsequently discontinued by 10 weeks of life. Genetic analysis revealed a novel heterozygous *INSR* missense variant p.(Arg1119Gln) in the affected twin and the mother. **Family 3:** A SGA child presented with diazoxide responsive HH. Diazoxide was gradually weaned and discontinued by 9 weeks of age. Genetic analysis revealed a novel heterozygous *INSR* p.(Arg1191Gln) variant in the proband and her father. We report, for the first time, an association of *INSR* mutation with neonatal HH responsive to diazoxide therapy that resolved subsequently. Our case series emphasizes the need for genetic analysis and long-term follow up of these patients.

Keywords: *INSR* mutation, congenital hyperinsulinism, neonatal hyperinsulinemic hypoglycaemia, familial diabetes mellitus

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Introduction:

Insulin receptor is a trans-membrane receptor from tyrosine kinase family where insulin binds to two distinct sites on each subunit of the receptor (1, 2). Insulin receptor mutations are associated with severe insulin resistance phenotypes, such as Rabson-Mendenhall, Donohue and type A insulin resistance syndrome (3, 4). Rabson-Mendenhall and Donohue syndromes are recessively inherited conditions leading to decreased expression of receptor, blockage of receptor transport to the plasma membrane or decreased insulin binding, associated with extreme insulin resistance. Type A insulin resistance is associated with mono allelic *INSR* missense mutations, which cause a less severe phenotype and are most likely to occur within the tyrosine kinase domain (4).

Insulin is an anabolic peptide hormone secreted by the beta cells of pancreatic islets. Inappropriate secretion of insulin leads to persistent/recurrent hypoglycaemia (hyperinsulinemic hypoglycaemia, HH), which can result from a mutation in a number of different genes (5, 6).

There are several reports of autosomal dominant heterozygous *INSR* mutations causing hypoglycaemia in adults but to the best of our knowledge there is no data about heterozygous *INSR* mutations causing neonatal HH (7-12).

In this study, we report three different families presenting with variable clinical manifestations ranging from neonatal HH to adult onset type 2 diabetes mellitus associated with heterozygous *INSR* mutation.

Case Report:

Family 1:

A 13-day-old female baby (proband) was referred to the tertiary endocrine unit with persistent neonatal hypoglycaemia since 3 hours of life (capillary blood glucose: 1.9mmol/l). She was born by emergency caesarean section due to breech presentation at 37 weeks gestation, weighing 2.41kg (-2.42 SDS) and measuring 47cm in length (-1.15 SDS). There was a history of gestational diabetes in the mother requiring insulin treatment. The hypoglycaemia was initially managed with high concentration dextrose containing fluids (glucose infusion rate (GIR): 18.1mg/kg/min) and intravenous glucagon (10mcg/kg/hr) infusion. HH was confirmed on hypoglycaemia screen (Table 1). The echocardiogram was normal and she was subsequently commenced on oral diazoxide at 5mg/kg/day and chlorothiazide at 7mg/kg/day. She responded well to diazoxide which enabled weaning off the intravenous fluids and intravenous glucagon. She was fully established on oral feeds prior to discharge. During subsequent follow up, the diazoxide and chlorothiazide were slowly weaned and fully discontinued by 8 months of age following which a 16-hour controlled fast showed complete resolution of HH (Table 2).

The second child was born at 38 week of gestation by elective caesarean, weighing 2.43kg (-2.35 SDS) and measuring 48cm in length (-0.62 SDS). There was no history of birth asphyxia. The mother developed gestational diabetes once again but did not require insulin treatment unlike the previous pregnancy. At 10 hours of age she had symptomatic hypoglycaemia (capillary blood glucose: 1.9mmol/l) and was managed with intravenous dextrose containing fluids [GIR of 11.5mg/kg/min]. At 48 hours of age, a hypoglycaemia screen (Table 1) was undertaken which confirmed HH. Echocardiogram did not reveal any underlying cardiac abnormality. Diazoxide was started at 3mg/kg/day to achieve normoglycaemia. Oral chlorothiazide (7mg/kg/day) was added in conjunction with diazoxide. The intravenous fluids and glucagon were gradually weaned and the patient was established on full enteral feeds prior to discharge. During subsequent follow up, the diazoxide and chlorothiazide were slowly weaned and fully discontinued by 11 months of age, following which she underwent a controlled fast appropriate for age which confirmed the resolution of HH (Table 2).

The proband's mother had gestational diabetes mellitus during both pregnancies, requiring insulin treatment during the first pregnancy. She had normal body mass index (BMI 24 kg/m²) and had no features of insulin resistance [such as acanthosis nigricans], previous menstrual abnormalities or hirsutism. Proband's maternal grandfather (BMI 25 kg/m²) was diagnosed with type 2 diabetes mellitus at the age of 45 years and was treated with metformin. On examination he did not have any signs of insulin resistance or any history of hypoglycaemia.

Targeted next generation sequencing of the known hyperinsulinism genes identified a novel heterozygous *INSR* variant p.(Met1180Lys) (c.3539T>A) in the proband, her sister, mother and maternal grandfather. No further disease-causing variants were identified. (Figure 1)

Family 2:

The proband was a twin preterm (36 weeks gestation) born to a non-consanguineous parents by elective LSCS with a birth weight of 2.025kg (-3.75 SDS). Hypoglycaemia was recorded on 1st day of life (capillary blood glucose 1.1mmol/l). There was no history of birth asphyxia. The second twin had a birth weight of 2.56 kg (-1.95 SDS) and did not have any hypoglycaemia during the neonatal period. There was a maternal history of hypothyroidism, which was well controlled on thyroxine. The hypoglycaemia was initially managed with high concentration dextrose containing fluids (glucose infusion rate (GIR): 15.2mg/kg/min) and intravenous glucagon (10mcg/kg/hr) infusion. The hypoglycaemia screen (Table 1) confirmed HH. Echocardiography revealed moderate pulmonary stenosis and small patent foramen ovale. The child was subsequently commenced on diazoxide at 7.5mg/kg/day and spironolactone at 2mg/kg/day. He responded well to diazoxide which enabled weaning off the intravenous fluids and intravenous glucagon. He was fully established on formula feeds prior to discharge. During subsequent follow up, the diazoxide and spironolactone were slowly weaned and fully discontinued by 10 weeks of age.

The proband's elder sibling is a 3 year-old healthy girl with no history of neonatal hypoglycaemia. The proband's mother did not have any symptoms related to hypoglycaemia and was able to fast for prolonged hours during Ramadan. She had a normal BMI, no signs of insulin resistance [such as acanthosis nigricans] and there was no previous history of menstrual abnormalities or hirsutism. There was a history of type 2 diabetes in the maternal grandfather and maternal great grandmother.

Targeted next generation sequencing of the known HI genes identified a novel heterozygous *INSR* variant p.(Arg1119Gln) (c.3356G>A) in the proband and her mother. No further disease-causing variants were identified. Samples from the twin and older sister were not available for testing (Figure 1).

Family 3:

The proband was born at 37 week of gestation, weighing 2.20kg (-1.51 SDS). There was no history of birth asphyxia. At few hours of age she developed symptomatic hypoglycaemia (capillary blood glucose: 1.1mmol/l) and was managed with intravenous dextrose containing fluids. At 48 hours of age, a hypoglycaemia screen (Table 1) was undertaken which confirmed HH. Echocardiogram did not reveal any underlying cardiac abnormality. Diazoxide (5mg/kg/day) in conjunction with chlorothiazide (7mg/kg/day) was started. The intravenous fluids and glucagon were gradually weaned and the patient was established on full enteral feeds prior to discharge. During subsequent follow up, the diazoxide and chlorothiazide were slowly weaned and fully discontinued by 9 weeks of age.

The proband's father had a normal BMI and did not have any symptoms related to insulin resistance (acanthosis nigricans) or glucose variability (HbA1c: 36 mmol/l, fasting glucose: 4.6 mmol/l). Proband has two elder siblings who did not have any hypoglycaemia or symptoms related to insulin resistance. Targeted next generation sequencing of the known hyperinsulinism genes identified a novel heterozygous *INSR* variant p.(Arg1191Gln) (c.3572G>A) in the proband and her father. No further disease-causing variants were identified (Figure 1).

Discussion

The human insulin receptor is a heterotetramer composed of two α and two β subunits. The α subunit is entirely extracellular and the β subunit has extracellular, transcellular and intracellular domain that expresses tyrosine kinase activity. Insulin binds to α subunits and stimulates β subunit auto phosphorylation and kinase activity (1, 2). A single gene *INSR* located at 19p13.2 of 22 exon length codes for both α and β subunits (13). Homozygous and compound heterozygous mutations in *INSR* lead to severe insulin resistance (Donohue syndrome, Rabson-Mendenhall syndrome), whereas the heterozygous mutations in *INSR* cause the milder phenotype of insulin resistance syndrome (14, 15).

Heterozygous mutations in *INSR* cause insulin resistance in coexistence with hypoglycaemia, which may be due to selective impairment of insulin receptor function in skeletal muscle causing defective peripheral glycogen formation and insulin resistance whilst the preserved insulin receptor function in the liver leads to suppressed hepatic glucose production causing hypoglycaemia (10, 16). This is possibly due to the differential effect of insulin on the phosphorylation of the insulin receptor substrates (IRS) -1 and -2 in the skeletal muscle and liver (16). IRS-2 is constitutively phosphorylated due to the increased binding of the kinase regulatory loop binding domain of IRS-2 to the mutated receptor, preventing further activation by insulin or insulin-like growth factor (IGF) 1 in the muscles, whereas IRS-1 phosphorylation is normally activated by basal as well stimulated levels of insulin (17). This would explain the relative insulin resistance in the skeletal muscle in contrast to the insulin sensitivity in the liver.

Only a few patients with a heterozygous *INSR* mutation associated with episodes of hypoglycaemia have been reported (Table 3), mainly demonstrating post-prandial hypoglycaemia following oral glucose tolerance test (8,9). Symptomatic fasting hypoglycaemia has been reported in a few patients; however age appropriate controlled fasts were not undertaken (8-11). Symptomatic hypoglycaemia is reported to have occurred as young as three years of age in one patient however HH was not confirmed (7). The signs of insulin resistance were noted in most of these patients while there is only minimal information provided about the individual family members. Enkhtuvshin et al reported a heterozygous *INSR* mutation associated with type 2 diabetes mellitus in a mother and transient hypoglycaemia in both children at birth with the same mutation, however hyperinsulinemia was not documented and hypoglycaemia resolved within 10 hours in both the siblings (18).

There have been several reported cases associated with homozygous or compound heterozygous mutations causing Donohue syndrome (complete absence of functional insulin receptors) and leading to fasting hypoglycaemia which has been suggested as the effect of insulin on type 1 IGF receptors (19). However type 1 IGF receptors disappear from the liver in adult life (20), which doesn't explain the several reported cases of hypoglycaemia in adult life associated with heterozygous *INSR* mutations (Table.3).

Neonatal HH has not been previously reported in association with heterozygous *INSR* mutations (7-11). The precise mechanism by which these mutations lead to diazoxide responsive neonatal HH, which resolves in infancy, is not clear. One of the possible explanations could be the effect of high levels of insulin on type 1 IGF receptors in the neonatal period with subsequent resolution of hypoglycaemia due to β -cell exhaustion and potential developmental changes in the expression of IGF1 receptor (21, 22). In adults, the deposition of amyloid in the pancreas has been observed following chronic insulin resistance, which subsequently leads to type 2 diabetes mellitus (23).

In our study, among all three families, affected children were small for gestational age similar to the previously reported patients (9, 18). Since insulin has a central role in controlling foetal growth, genetic factors, which impair insulin secretion or action, would be expected to reduce foetal growth. This has been demonstrated experimentally in transgenic mice lacking key intermediates of the insulin-signalling pathway (24). In our study, the affected adult family members were constitutionally lean, which suggests that peripheral insulin resistance might not only prevent the glycogen storage in muscles, but also reduce lipogenesis and increase lipolysis in the fat cells (9).

Although signs of insulin resistance such as acanthosis nigricans and symptoms of androgen excess such as menstrual abnormalities and hirsutism are common in patients with *INSR* mutation, the families we describe did not have any such signs or symptoms, supporting the notion that different mutations in *INSR* lead to different phenotypes.

Unfortunately we did not have access to the insulin levels in the adult members of the families. Moreover, a common heterozygous mutation, p.Arg1174Gln, has been described to be associated with variable clinical phenotypes within the members of the same family (7).

Apart from the genetic background, the phenotype could also be influenced by the environmental factors. Patients with insulin resistance and compensatory increase in insulin secretion may develop diabetes mellitus in later life when the ability to secrete insulin declines. This leads to postprandial glucose intolerance, followed by fasting hyperglycaemia and diabetes mellitus, which might be prevented by early interventions that include dietary and behavioural modifications. These observations suggest that patients with *INSR* mutation need to be followed up long term for other manifestations in later life.

Diazoxide is the first line treatment for CHI, which works as an agonist at KATP channel leading to termination of Ca^{+} dependent insulin release (25), however there is no data regarding the use of diazoxide in individuals with an *INSR* mutation causing neonatal HH. *INSR* mutations lead to high insulin levels due to insulin resistance and metformin has been used effectively in the adult population (10, 11) although the mechanism is not clear. Avoidance of high glycaemic index foods may improve symptoms in the patients with post-prandial hypoglycaemia (11).

Conclusion

We are reporting the first series of heterozygous *INSR* gene mutations causing neonatal HH. This study also highlights that the same gene mutation can lead to variable phenotype within the same family members. Hence, a detailed genetic testing in the family is essential for long-term follow up. All our patients followed a relatively benign clinical course during infancy and the hyperinsulinism resolved in the first year of life but further monitoring will inform us of the clinical course through the adult life. There is no consensus about the treatment of children with *INSR* mutations due to its rarity, but lifestyle modification could play a key role in the long-term management.

Informed Consent: Informed consent was obtained from the parents of the patients for publication of this case series.

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Table 1: Biochemical parameters during the hypoglycemic episode

Hypo Screen	Family 1		Family 2	Family 3
	Proband	Sibling	Proband	Proband
Lab Glucose (3.5-5.5 mmol/l)	1.4	1.8	2.01	1.9

Insulin (pmol/l)	>644.4	408	315	56
C-peptide (pmol/l)	1463	663	523	503
Plasma Free Fatty Acid (umol/l)	382	207	-	-
3-hydroxybutyrate (umol/l)	80	24	-	-
Cortisol (nmol/l)	364	416	415	-

Table 2: Biochemical evaluation at the end of 16 hour controlled fast

Hypo Screen	Family 1	
	Proband	Sibling
Lab Glucose (3.5-5.5 mmol/l)	4.4	3.4
Insulin (pmol/l)	74	74
C-peptide (pmol/l)	189	283
Plasma Free Fatty Acid (umol/l)	1362	714
3-hydroxybutyrate (umol/l)	845	348

Table 3: List of reported patients with hypoglycemia associated with heterozygous *INSR* mutation.

Reference	<i>INSR</i> location	Amino acid change (HGVS nomenclature)	Age of presentation (years)	Reported fasting hypoglycemia	Reported post-prandial Hypoglycemia	Plasma Glucose (mmol/l)	Corresponding Serum Insulin (pmol/l)	Other clinical features	Treatment	Outcome
Our patient	Exon 20	p.(Met1180Lys)	Newborn	Yes	No	1.4 (F)	>694.4	SGA	Diazoxide	Resolution of

(Family 1)			(Proband)							hypoglycemia (medication stopped)
			Newborn (Sibling)	Yes	No	1.8 (F)	408	SGA	Diazoxide	
Family 2		p.(Arg1119Gln)	Newborn	Yes	No	2.0 (F)	315.2	SGA	Diazoxide	
Family 3		p.(Arg1191Gln)	Newborn	Yes	No	1.9 (F)	56.2	SGA	Diazoxide	
Innaurato et al (8)		p.(Phe1213Leu)	11	No	Yes	3.0 (PP)	598.6	AN	-	-
			36 (Mother)	No	No	1.9 (PP)	295.8	-	-	-
			19 (Brother)	No	No	2.2 (PP)	588.2	-	-	-
Preumont V et al (10)		p.(Met1180Val)	16	No	Yes	3.4 (F)	604	AN, PA, HR	Metformin	Reduction in hypoglycemia
			48 (Mother)	-	-	2.4 (?)	355	OG	Metformin	Reduction in hypoglycemia
		p.(Arg1201Gln)	43	No	Yes	3.2 (PP)	1337	No s/o IR	Metformin	Reduction in hypoglycemia
Krishnamurthy M et al (11)		p.(Arg1131Trp)	12	Yes	No	5.8 (F)	698	AN, HR, CL	Metformin	Reduction in hypoglycemia
Huang Z et al (9)	Exon 20	p.(Arg1174Trp)	16	Yes	No	2.6 (PP)	2090	AN, OG	-	-
			8 (brother)	-	-	1.9 (PP)	467	SGA (2.4kg)	-	-
Hojlund K et al*(7)	Exon 20	p.(Arg1174Gln)	12	No	Yes	3.3 (F)	360	OG	-	-
Enkhtuvshin et al (18)	Exon 17	Δ Leu999	Newborn	-	-	1.1	-	SGA (2.2 kg)	-	Resolution at 10 hours of life
			Newborn (sibling)	-	-	1.2	-	Birth weight: 2.5 kg	-	Resolution at 3 hours of life

AN: Acanthosis Nigricans, PA: Primary Amenorrhea, OG: Oligomenorrhea, HR: Hirsutism, CL: Clitoromegaly, s/o: signs of, IR: insulin Resistance, F: fasting, PP: post-prandial, SGA – small for gestational age

*Other 8 family members were also reported with hypoglycemia and same mutation

Figure 1: Pedigree chart showing autosomal dominant inheritance in the families; circle denotes females, square males. The proband is indicated by arrow mark in each family, dotted symbol denote person with diabetes with unknown mutation status and solid symbols denote affected subjects with (Family 1) *INSR* gene p.(Met1180Lys) or (Family 2) *INSR* gene p.(Arg1119Gln) or (Family 3) *INSR* gene c.3572G>A, p.(Arg1191Gln) mutation.

Family 1

Family 2

Family 3

Uncorrected proof