ECRONICON OPEN ACCESS

EC PAEDIATRICS
Case Report

A Novel ABCC8 Gene Mutation in a Newborn with Persistent Congenital Hyperinsulinism (CHI)

Ahmed Elmelhat[1], Manal Mustafa[2], Mohamed Abou Seif Badawi[1]* and Ahmed Elbosraty[1]

[1]Department of Pediatrics, NICU, Latifa Women and Children hospital (LWCH), Dubai, United Arab of Emirates

[2]Department of Pediatrics, Endocrinology Unit, Latifa Women and Children hospital (LWCH), Dubai, United Arab of Emirates

***Corresponding Author:** Mohamed Abou Seif Badawi, Department of Pediatrics, NICU, Latifa Women and Children hospital (LWCH), Dubai, United Arab of Emirates.

Received: October 21, 2019; **Published:** November 11, 2019

Abstract

Persistent neonatal hypoglycemia is one of the frequently encountered presentations in the neonatal intensive care unit. Its major long-term sequelae that include neurologic damage resulting in mental retardation, seizure activity, developmental delay, and personality disorders mandate rigorous work up to define its causes. We report a novel gene mutation for persistent hyperinsulinemic hypoglycemia and its management.

Keywords: *Hypoglycemia; Neonatal; Congenital Hyperinsulinemia*

Introduction

Neonatal hypoglycemia is the most common metabolic problem in newborns. The overall incidence has been estimated at 1 to 5 per 1,000 live births, but it is higher (up to 30%) in high risk populations. It can present in either transient or persistent and recurrent forms. Transient neonatal hypoglycemia responds readily to treatment, is associated with an excellent prognosis. However Persistent hypoglycemia is more likely to be associated with possible neurological sequelae. Metabolic and endocrine abnormalities can cause persistent hypoglycemia. Persistent congenital hyperinsulinism occurs because of abnormal insulin secretion from β cells of the pancreas. Genetic testing is the definite diagnosis for such condition. Here we are reporting a novel gene mutation as one of the causes of persistent congenital hyperinsulinism.

Case Report

A female baby weighing 4.125 kg was born at 39 weeks to G3P3, 25 years old, Rubella immune mother with negative serology. She was a product of 1st degree consanguineous marriage, with uneventful pregnancy. Antenatal ultrasound scan was normal, maternal high vaginal swab and midstream urine sample showed no growth.. There were positive family history of early neonatal deaths in their home country.

She was delivered by normal vaginal delivery through clear liquor, cried immediately after birth with Apgar score of 8/9 at 1/5 minutes respectively. Soon after delivery she was allowed direct skin to skin contact and started breast-feeding successfully. Being large for gestational age, monitoring of her blood sugar was started and at 1 hour age, it was 23 mg/dl (1.27 mmol/L). She was managed according

to our hypoglycemia protocol and transferred to the neonatal intensive care unit (NICU) for further management.

She was started on IV fluids. As her blood glucose was not maintained, so glucose infusion rate (GIR) was increased gradually to maximum GIR of 20 mg/kg/minute. She was kept nil per mouth in view of difficulties of controlling her blood sugar and the need of high concentration of GIR.

Sepsis was excluded clinically and by negative sepsis screening. Thyroid, Liver and kidney function tests were normal. Ultrasound abdomen was normal.

Assays (normal values)	Critical Sample Day 5	Critical Sample Day 10
Serum glucose (3.6 - 7.7mmol/l)	22 mg/dl (1.22 mmol/L)	33 mg/dl (1.8 mg/dl)
Serum insulin (< 2 µU/ml)	16.2	20.6
C-peptide (1.8 - 4.7 ng/ml)	5.7	5.2
Serum Cortisol (68 - 328 nmol/l)	161	Not repeated
Growth hormone (0 - 8 ng/ml)	> 40.0	Not repeated
Free Fatty acid (0.1-0.6 mEq/L)	0.0 (low)	Not repeated
Urine Ketones and reducing substances	Negative	Negative

Table 1: *Critical samples done on day 5 and day 10 of life.*

Critical sample during a hypoglycemic episode was sent on 2 occasions and the results are shown in table 1.

Her insulin levels and C-peptide were significantly high on two hypoglycemic occasions, which confirmed the diagnosis of Congenital Hyperinsulinemic Hypoglycemia of Infancy. Positron emission tomography (PET) scan of the pancreas to delineate the type of hyperinsulinemia (focal or diffuse) was not available throughout our country; therefore Molecular genetic testing was done which showed mutation

Gene	ABCC8
Variant description (HGVS)	NM_001287174:c.3644G>T (p.Arg1215Leu)
Variant location; GRCh37 (hg19)	Chr11(GRCh37):g.17424217C>A
Variant classification: (Pathogenic/Likely pathogenic/Uncertain significance/Likely benign/Benign)	Likely pathogenic

Table 2: *Results of the molecular genetic testing.*

of the ABCC8 gene. She was homozygous for a pathogenic ABCC8 missense variant, p.R1215L. This result is consistent with diagnosis of autosomal recessive congenital hyperinsulinism with diffuse pancreatic disease (Table 2).

In addition to hypertonic glucose infusion and different feeding protocols, she was given a trial of oral Diazoxide for 7 days that started on day 16 of life with initial dose 5 mg/kg/day every 8 hours that was maximized to 15 mg/kg/day every 8 hours, however it was discontinued due to poor response.

In view of poor response to the 1st line of persistent hyperinsulinemic hypoglycemia treatment protocol, she was given a trial of the 2nd line of treatment. Glucagon was given intramuscular during the attacks of hypoglycemia. On day 23 of life, Octreotide (Somatostatin

analogue) started initially as 10 mcg/kg/dose subcutaneously every 8 hours that increased to 20 mcg/kg/dose every 6 hours. However, Tachyphylaxis developed to Octreotide so, Glucagon intravenous infusion was started initially with, a dose of 0.005 mg/kg/hour then increased to maximum dose of 0.05 mg/kg/hour. In addition, Octreotide changed simultaneously to continuous IV infusion in a dose of 0.1 mcg/kg/hour.

In view of complexity of her blood sugar control, her feeding was introduced gradually based on her blood sugar monitoring; different feeding regimens were tried under the supervision of pediatric dietician. A 2 hourly and 3 hourly feeding were tried with added Polycose glucose polymers (hydrolyzed cornstarch) with each feed. However, she responded to continuous Naso-gastric tube with the added hydrolyzed cornstarch that reached its maximum dosing of 2 grams/70 ml of milk.

Use of mTOR inhibitors (Sirolimus) was not started due to its serious side effects and uncertainty about benefit.

At the age of 3 months, she underwent laparoscopic near total pancreatectomy (95% of the pancreas was resected). Post-operative she was requiring Octreotide subcutaneously 6 hourly with bolus feeding every 3 - 4 hours. Her blood sugar readings improved with occasional hypoglycemia and hyperglycemic attacks. She was discharged home on subcutaneous injection of octreotide with special feeding protocol and advised for close follow up in the pediatric endocrinology, neurology and dietician clinic. Her Brain MRI prior to discharge was normal.

Discussion

Maternal conditions	Diabetes in pregnancy (pre-gestational/gestational) Medications (β-blockers)
Neonatal conditions	Prematurity Intrauterine Growth Retardation (IUGR) Small for gestational age (SGA) Large for gestational age (LGA) Perinatal asphyxia Hemolytic disease of newborn Neonatal sepsis Polycythemia Post-exchange transfusion Parenteral nutrition

Table 3: *Risk factors for transient neonatal hypoglycemia.*

Among the neonatal intensive care units, there is no agreement about the definition of neonatal hypoglycemia. However, each unit must have their own definition to allow for the standard care. Our neonatal unit guidelines define hypoglycemia as Plasma Glucose (PG)

Endocrine disorders	• Hyperinsulinism • Primary- mutations in ABCC8, • KCNJ11, GCK, HADH, SCL16A1, HNF4A, UCP2 gene • Secondary- Infants of Diabetic Mother (IDM) • Hypopituitarism • Isolated growth hormone deficiency • Adrenal disorders- Congenital adrenal hyperplasia, ACTH deficiency, Familial glucocorticoid deficiency, Cortisol deficiency
Disorders of gluconeogenesis	• Fructose-1,6 bisphosphates deficiency • Phosphoenolpyruvate carboxykinase deficiency • Pyruvate carboxylase deficiency
Disorders of galactose metabolism	• Galactosemia
Disorders of fructose metabolism	• Hereditary fructose intolerance
Disorders of hepatic glycogen synthesis	• Glycogen storage disease
Disorders of fatty acid metabolism	• Defects in β-oxidation • MCAD deficiency • LCHAD deficiency • SCHAD deficiency
Disorders of amino acid metabolism	• Maple syrup urine disease • Propionic academia • Methylmalonic acidemia • Tyrosinemia
Disorders of carnitine metabolism	• Primary carnitine deficiency • CPT-I deficiency • CACT deficiency • CPT-II deficiency
Glucose transporter defects	• GLUT 1/2/3 transporter defects
Ketogenesis and ketone body utilization defects	• HMG CoA synthase deficiency • HMG CoA lyase deficiency • *β*-ketothiolase deficiency • SCOT deficiency

Table 4: *Endocrine and metabolic causes of persistent neonatal hypoglycemia*

ACTH: Adrenocorticotropic Hormone; CACT: Carnitine-Acylcarnitine Translocase; CPT: Carnitine Palmitoyltransferase; LCHAD: Long-Chain 3-Hydroxyacyl-Coenzyme A Dehydrogenase; MCAD: Medium-Chain Acyl-Coa Dehydrogenase; SCHAD: 3-Hydroxyacyl- Coenzyme A Dehydrogenase; SCOT: Succinyl-CoA: 3-Ketoacid-Coenzyme A Transferase1.

values < 2.2 mmol/L (40 mg/dl) in first 24 hours and < 2.8 mmol/L (50 mg/dl) after 24 hours of life. Transient neonatal hypoglycemia occurs during first few hours of life because of slow or immature fasting adaptation process. Table 3 shows the causes of transient hypo-

Blood insulin	> 1-2 µU/mL
Glucose infusion rate to maintain euglycemia (mg/kg/min)	> 7 (before 6 mo) 3 - 7 (after 6 mo)
Blood β-hydroxybutyrate (BHB)	< 2 mmol/L (2000 µmol/L)
Blood free fatty acids (FFA, NEFA)	< 1.5 mmol/L (1.5 mEq/L)
Glycemic response by 0.5–1 mg glucagon (IM, IV)	> 30 - 40 mg/dL (15 - 45 min)

Table 5: *Diagnostic criteria of hyperinsulinemic hypoglycemia (at blood glucose < 50 mg/dl).*
Definite: ≥ 2 of the criteria, or one of the criteria + identification of a mutation in one of the known causative genes.
Possible: one of the criteria.

glycemia [1].

Persistent neonatal hypoglycemia defined as persistent hypoglycemia beyond the first 48 hours of life or the requirement of glucose infusion > 12 mg/kg/min to maintain euglycemia beyond 48 hours of life. Table 4 shows causes of persistent hypoglycemia [2].

Diagnosis of CHI is based on the finding of inappropriate relative hyperinsulinemia in the context of hypoglycemia. Table 5 shows the diagnostic criteria.

There are two forms of CHI: a transient form, which develops soon after birth and frequently resolves by 3 - 4 months of age, and a persistent form, with a more prolonged duration. In some cases, the symptoms of persistent CHI may manifest after infancy.

Mutations in nine different genes regulating insulin secretion (ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A, HNF1A and UCP2) have been identified in patients with CHI. The ATP-sensitive potassium channel (K_{ATP} channel) regulates the release of insulin from pancreatic beta cells, which are located on chromosome 11p14-15.1. It is composed of four regulatory subunits (SUR1, encoded by the *ABCC8* gene) and a small subunit (Kir6.2, encoded by the *KCNJ11* gene) that surrounds a central pore [3].

Inactivating mutations in *ABCC8* have autosomal recessive patterns of inheritance that result in lack of K_{ATP} channel activity and intractable hypoglycemia, with poor response to Diazoxide. Many of these patients will require partial or near-total pancreatectomy [4].

There is some evidence that these mutations also lead to activation of the mTOR pathway (mammalian target of rapamycin complex), which promotes beta cell proliferation. This could explain the diffuse nature of the islet abnormalities in those cases. It also provides the mechanism for treatment of CHI with the mTOR inhibitor, Sirolimus [5].

Treatment encompass both the medical treatment and eventually the surgical treatment in case normoglycemia cannot be maintained by medical treatment, to avoid neurological sequelae.

Medical treatment for CHI includes the first line and the 2nd line treatment in case the former does not control the hypoglycemia. The aim is to maintain PG > 3.8 mmo/l (65 - 70 mg/dl). The 1st line entails continuous glucose infusion followed by nutritional support once blood sugar maintained and the use of diazoxide in case the above two measures did not maintain the euglycemia.

The 2nd line treatment involves the use of octreotide and or glucagon. Nutritional support involves frequent feeding or continuous feed-

ing of expressed breast milk in addition to cornstarch (preferred after 9 mo), or formula for glycogen storage diseases.

Diazoxide is benzothiazine derivative which is a potent β-cell K_{ATP} channel opener. The stabilization of opened K_{ATP} channels leads to the inhibition of insulin secretion. Patients with known or suspected genetic defect of the SUR and Kir 6.2 subunits may not fully respond to Diazoxide therapy [6].

Somatostatin (Octreotide) is a cyclic polypeptide that is found throughout the nervous and gastrointestinal system. It has inhibitory effects on the release of glucagon and insulin from the pancreatic islet cells and suppresses the glucagon-like-peptide 1 (GLP-1) [7]. Other actions include inhibition of gastrointestinal motility, gallbladder contractility and splanchnic blood flow. Octreotide is used off-label in children < 6 years of age for hyperinsulinism, chylothorax, and gastrointestinal bleeding. Side effects include tachyphylaxis (loss of effect during prolonged treatment), gastrointestinal symptoms, gall stones, hepatitis, necrotizing enterocolitis and growth deceleration [8].

It is worth mentioning that even in patients with persistent CHI, the severity of hypoglycemia tends to improve over time and patients often achieve spontaneous remission without the need for medical treatment. However, remission may require several months to several years, and some patients still require treatment after adulthood. Diabetes mellitus can develop after medical treatment, although the incidence is much lower when compared with patients following subtotal pancreatectomy [10,11].

Surgery for hyperinsulinemic hypoglycemia is the final treatment once medical treatment fails to control euglycemia; however, it represents an acute transition from a hyperinsulinemic state to a diabetic status. Different modalities of surgical treatment are available including partial pancreatectomy when focal lesion are identified in the pancreas by the PET scan or in case of diffuse lesion the removal of 85%, 95% or 98% of the pancreatic tissues.

Endocrine function becomes severely affected in most patients postoperatively. For example, among more than 300 children with hyperinsulinemic hypoglycemia treated with near-total pancreatectomy, 96% had developed insulin-dependent diabetes by 11 years after surgery [8].

Exocrine function is also impaired in most patients after near-total pancreatectomy, and about half have clinically significant fat malabsorption, with symptoms including steatorrhea and poor weight gain that respond to pancreatic enzyme replacement. Long-term follow up is needed after surgery for both endocrine and exocrine functions, which may need insulin therapy and replacement therapies respectively [9].

To the best of our knowledge, this mutation is a novel mutation in the ABCC8 gene for autosomal recessive congenital hyperinsulinism and diffuse pancreatic disease.

Conclusion

The diagnosis of persistent CHI depends on specific diagnostic criteria in addition to if available the use of mutational genetic analysis. The underlying mutation will assist in understanding the disease course and guide the treatment. Both the medical and surgical treatment aim at close monitoring of plasma glucose to maintain it in an acceptable level to avoid the long term neurological and developmental sequelae. The management of neonates with persistent CHI includes the multidisciplinary team work involving but not limited to the nursing staff, neonatologist, pediatric endocrinology, clinical pharmacist, pediatric nutritionist and the pediatric surgeon.

Acknowledgement

University of Exeter Medical School, Sarah Flangan, M.D, UK. For their help and accepting processing the sample for the detailed genetic study.

Statement of Ethics

A written consent was taken from parents.

Disclosure Statement

There is no conflict of interest of any of the authors with the results of this case study.

Funding Sources

No funding was received.

Bibliography

1. Stanley C., *et al*. "Re-evaluating "transitional neonatal hypoglycemia": mechanism and implications for management". *Journal of Pediatrics* 166.6 (2015): 1520-1525.

2. Cryer P., *et al*. "Evaluation and management of adult hypoglycemic disorders: an Endocrine Society clinical practice guideline". *Journal of Clinical Endocrinology and Metabolism* 94.3 (2009): 709-728.

3. Pinney S., *et al*. "Clinical characteristics and biochemical mechanisms of congenital hyperinsulinism associated with dominant KATP channel mutations". *Journal of Clinical Investigation* 118.8 (2008): 2877-2886.

4. Flanagan S., *et al*. "Dominantly acting ABCC8 mutations in patients with medically unresponsive hyperinsulinaemic hypoglycaemia". *Clinical Genetics* 79.6 (2011): 582-587.

5. Alexandrescu S., *et al*. "Persistent hyperinsulinemic hypoglycemia of infancy: constitutive activation of the mTOR pathway with associated exocrine-islet transdifferentiation and therapeutic implications". *International Journal of Clinical and Experimental Pathology* 3.7 (2010): 691-705.

6. Peranteau W., *et al*. "Prenatal diagnosis and postnatal management of diffuse congenital hyper-insulinism: a case report". *Fetal Diagnosis and Therapy* 21.6 (2006): 515-518.

7. Plockinger U., *et al*. "Octreotide suppresses the incretin glucagon-like peptide (7-36) amide in patients with acromegaly or clinically nonfunctioning pituitary tumors and in healthy subjects". *European Journal of Endocrinology* 140.6 (1999): 538-544.

8. Lamberts SW., *et al*. "Octreotide". *New England Journal of Medicine* 334.4 (1996): 246-254.

9. Yorifuji T., *et al*. "Clinical practice guidelines for congenital hyperinsulinism". *Clinical Pediatric Endocrinology* 26.3 (2017): 127-152.

10. Mohamed Z., *et al*. "Hyperinsulinaemic hypoglycaemia: genetic mechanisms, diagnosis and management". *Journal of Clinical Research in Pediatric Endocrinology* 35.4 (2012): 169-181.

11. Welters A., *et al*. "Long-term medical treatment in congenital hyperinsulinism: a descriptive analysis in a large cohort of patients from different clinical centers". *Orphanet Journal of Rare Diseases* 10 (2015): 150.

Volume 8 Issue 12 December 2019