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A Novel Intragenic *SLC16A1* Mutation Associated With Congenital Hyperinsulinism

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Introduction

Congenital hyperinsulinism, characterized by excessive and dysregulated insulin secretion, is the most common cause of persistent hypoglycemia in children. Delay in the diagnosis and/or treatment can lead to significant neurodevelopmental sequelae, seizures, and potentially death. To date, mutations have been identified in 11 genes with one of them being *SLC16A1*, encoding monocarboxylate transporter-1 (MCT-1).[1] MCT-1 is a transporter protein regulating the transport of lactate and pyruvate, which are potent insulin secratogogs in β cells. There is a selective inhibition of MCT-1 expression in β cells to keep their intracellular concentration low. Promoter mutations in *SLC16A1* gene lead to increased expression of MCT-1 in β cells, and subsequent hyperinsulinism. Hyperinsulinemic hypoglycemia is usually exercise-induced and responsive to diazoxide.[2,3]

We report the first intragenic mutation in *SLC16A1* gene encoding MCT-1 in a child with congenital hyperinsulinism.

Case Presentation

A term, large for gestational age infant (birth weight 4130 g) was found to be hypoglycemic with blood glucose (BG) of 20 mg/dL soon after birth. He required repeated intravenous (IV) dextrose boluses due to persistent hypoglycemia and was transferred to the neonatal intensive care unit, where he was started on IV dextrose infusion. His neonatal intensive care unit stay was complicated by severe gastroesophageal reflux and necrotizing enterocolitis. He underwent sigmoid colon resection, Nissen fundoplication, and a gastrostomy tube (G-tube) insertion. During this period, he was on total parenteral nutrition providing a glucose infusion rate (GIR) of 12 mg/kg/min with no further episodes of hypoglycemia.

He was incidentally found to have bilateral adrenal hemorrhages on an ultrasound. His blood pressure was elevated without a clear etiology and was started on angiotensin-converting enzyme inhibitor. A brain magnetic resonance imaging, obtained due to poor oral skills, was normal. Additionally, he failed his hearing screen bilaterally. There was no fasting tolerance test performed prior to his discharge from outside facility at 3 months of age.

At 4 months of age, he had a seizure at home. His point-of-care (POC) BG was 36 mg/dL with a repeat of 40 mg/dL, and he was taken by ambulance to the emergency department. In the emergency department, his BG was 54 mg/dL; he received an IV dextrose bolus followed by a dextrose infusion with normalization of his BG.

Prior to his seizure, he was in his normal state of health. He was taking Elecare 24 kcal 4 oz every 3 hours by G-tube. His last feed was 2 hours prior to the seizure and well-tolerated. He did not have any history of seizures and there was no family history of seizures or hypoglycemia. His only medication was the angiotensin-converting enzyme inhibitor. He was developmentally delayed, with lack of head control and inability to roll at 4 months of age.

He weighed 6.46 kg (15th percentile) and measured 64 cm (32nd percentile). His physical exam was unremarkable with no dysmorphic features.

His baseline workup did not reveal any etiologies. A diagnostic fast was started after his 8 AM feed. He developed hypoglycemia (POC-BG 18 mg/dL) 1 hour later. A critical sample was drawn. The results were consistent with hyperinsulinemic hypoglycemia (Table 1).

Due to persistent hypoglycemia in the setting of hyperinsulinism, he was placed on intravenous fluid (IVF; GIR 8.8 mg/kg/min), diazoxide at 15 mg/kg/day

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Table 1. Initial Diagnostic Workup Along With Critical Laboratory Testing.

Initial Labs			Critical Labs		
	Value	Reference Ranges		Value	Reference Ranges
HCO_3	24 mmol/L	20-28	Glucose	41 mg/dL	50-120
Glucose	66 mg/dL	50-120	Insulin	6 mU/L	1.3-28.7
AM-Cortisol	43.3 μg/dL	2.8-23	C-peptide	2.79 ng/mL	0.8-5.2
AST	66 U/L	20-60	BOHB	0.13 mmol/L	<0.3[a]
ALT	73 U/L	6-50	FFA	0.16 mmol/L	≤0.73
Lactate	2.3 mmol/L	0.2-2.0			
Triglyceride	73 mg/dL	20-150	0.3 mg glucogan was given		
Uric acid	2.8 mg/dL	2.0-6.2	Glucose (30 minutes)	122 mg/dL	
Pyruvic acid	0.078 mmol/L	0.03-0.107	GH (2 hours)	8.4 ng/mL	
Plasma acylcarnitine analysis			Normal		
Plasma amino acid analysis			Normal		
Urine organic acid analysis			Elevated dicarboxylic acids, but no acylglycine conjugate were detected. Likely due to diet.		

Abbreviations: HCO_3, bicarbonate, AM-cortisol, early morning cortisol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BOHB, β-hydroxy butyrate; FFA, free fatty acid; GH, growth hormone.
[a]After 12 hours of fasting.

Q8H, and continuous G-tube feeding (GIR 6.7 mg/kg/min). IVF was gradually weaned off with stable BGs. Reinitiation of bolus feedings resulted in reappearance of hypoglycemia.

The repeated postprandial hypoglycemia raised concerns about dumping syndrome. Gastric emptying study showed rapid gastric emptying consistent with dumping syndrome. He successfully completed a 10-hour fast without any hypoglycemia. Diazoxide was discontinued, G-tube feeds were placed on hold, and he was placed on IVF (GIR 8 mg/kg/min) for the following 3 days. He was noted to have hypoketotic hypoglycemic episodes (POC BG 43 and 44 mg/dL) when there were interruptions in IVF secondary to IV access problem. Critical labs repeated in one of these episodes revealed the followings: serum glucose 53 mg/dL, insulin <1 mU/L, C-peptide 0.16 ng/mL, β-hydroxybutyrate 0.32 mmol/L. He was advanced on continuous G-tube feed while weaning down on IVF. F-DOPA positron emission tomography scan of pancreas did not show any focal lesion. Diazoxide was restarted at 20 mg/kg/day Q8H. He was transitioned to G-tube bolus feed during daytime and continuous feed overnight with stable BGs and later discharged home after passing safety fast.

Whole exome sequencing (Baylor Miraca Genetic Laboratories, Houston, TX) revealed a heterozygous variant of unknown significance in the *SLC16A1* gene (c.556C>G, p.L186V). In silico analysis using Polyphen-2 predicted this mutation to be probably damaging with a score of 0.999 in HumDiv and 0.973 in HumVar. The promotor region sequence analysis was not included in the whole exome sequencing. Parental genetic testing were not completed.

Discussion

We report the first intragenic mutation of MCT-1 in a child with congenital hyperinsulinism. Despite the diagnosis of dumping syndrome that contributed to hyperinsulinemic hypoglycemia, our patient's hypoglycemia persisted even on IV dextrose with lack of tolerance to brief interruptions in IV infusion leading to hypoketotic hypoglycemia.

The possibility of other hypoglycemic disorders was ruled out. He had normal newborn screen, urine organic acid, plasma acylcarnitine, and plasma aminoacids analyses. Additionally, glycogen storage disease is unlikely given the absence of hepatomegaly, normal triglycerides, uric acid, pyruvate and lactate, and only minimally elevated liver function tests. Cortisol deficiency was ruled out with normal morning cortisol. He had a decent growth hormone level on glucagon stimulation. Moreover, the immediate hypoglycemia following discontinuation of IV dextrose is inconsistent with other disorders as hypoglycemia associated with most other disorders occurs after some duration of fasting. The hypoglycemic episodes could be explained by hyperinsulinemic state. The lack of detectable insulin level at the time of hypoglycemia is not inconsistent with hyperinsulinism.[4] Indeed, there was a 20-minute lag between hypoglycemic episode and collection of the blood sample for insulin, which might have contributed to the undetectable level.

Whole exome sequencing revealed a "probably damaging" novel intragenic mutation in *SLC16A1* gene. Defects in this gene was previously reported as a cause of hyperinsulinemic hypoglycemia; however, the reported genetic alterations are limited to promoter region of this gene.[2] This mutation was found to be "probably damaging" by 97% to 99% confidence using in silico analysis software polyphen-2, which has a true positive prediction rates of 92% and 73% on HumDiv and HumVar data sets, respectively.[5] In the setting of clinical hyperinsulinism, we believe that this is a disease-causing mutation. Possible mechanisms include overexpression of the gene itself or baseline low-level expression of a mutant overactive transport protein due to this mutation. We speculate that the low-level expression of a mutant overactive protein may have led to increased transport of pyruvate into β cells and resulted in augmented insulin secretion. The ultimate proof requires functional studies by expressing this mutant gene in β cells and studying its effect.

Conclusion

We report the first intragenic mutation in *SLC16A1* in an infant with congenital hyperinsulinism. We speculate that this is a disease-causing mutation given the clinical picture. Further functional studies are needed to better understand the pathophysiology.

Author Contributions

MT: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

GSJ: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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