Case Report: Treatment of Hypoglycemia due to a Rare Pathogenic Variant in *AKT2* with Waxy Maize Heat-Modified Starch

Madeline Parker[1] and Daphne Yau[1]

[1]University of Saskatchewan

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Madeline Parker[1] & Daphne Yau[1]

[1] Department of Pediatrics, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Corresponding author:

Daphne Yau, MD MSc FRCPC

Pediatric Endocrinologist, Assistant Professor

University of Saskatchewan

Jim Pattison Children's Hospital

103 Hospital Drive

Saskatoon, SK

S7N 0W8

daphne.yau@usask.ca

(306) 655-2048 (tel), (306) 844-1536 (fax)

Abstract

Introduction: The serine-threonine kinase AKT2 is a critical mediator of insulin's anabolic effects, particularly cellular glucose uptake. The gain-of-function c.49G>A, p.(Glu17Lys)*AKT2* variant results in hypoketotic hypoglycemia with suppressed insulin and free fatty acid levels due to constitutive activation of the insulin signaling cascade. Although biochemical similarities exist amongst the eight individuals identified to date, the associated phenotype varies considerably. Treatment of these patients remains challenging, consisting primarily of frequent feeds with uncooked cornstarch.

Case Presentation: We describe a female with hemihypertrophy, developmental delay, and dysmorphic features who presented to our center with hypoglycemic seizures at age 6-months. Critical sample revealed hypoketotic hypoglycemia, undetectable insulin, and suppressed free fatty acids. Molecular testing confirmed a pathogenic c.49G>A, p.(Glu17Lys) *AKT2* mutation. Glycemic control was initially difficult to establish, with recurrent hypoglycemia despite high glucose infusion rates. Following in-hospital administration of

waxy maize heat-modified starch at age 4-years she remained euglycemic overnight, despite a previous report showing no benefit compared to uncooked cornstarch in an infant with the same mutation.

Conclusion: Our report suggests waxy maize heat-modified starch is a viable treatment option for patients with activating c.49G>A *AKT2* mutations and provides further evidence of a broad phenotypic spectrum.

Keywords: hypoglycemia, AKT2, starch

Key Clinical Message: The gain-of-function *AKT2*c.49G>A variant causes hypoketotic hypoglycemia with variable associated features. Due to lack of effective medications, treatment is primarily supportive. This report suggests waxy maize heat is a viable treatment option.

Introduction

Insulin's crucial role in energy metabolism is coordinated by a post-receptor signaling cascade resulting in activation of Akt2, a serine-threonine kinase. Expressed predominantly in insulin-sensitive tissue, Akt2 promotes glucose uptake by regulating translocation of the glucose transporter-4 (GLUT4) from cytoplasm to the cell membrane.[1] Further, Akt2 mediates insulin's metabolic effects by suppressing gluconeogenesis[1] and lipolysis[2], and stimulating lipogenesis.[3]

A growing body of evidence supports the clinical relevance of AKT2. Although rare, gain-of-function mutations in *AKT2* have been described in eight individuals with hypoketotic hypoglycemia.[4-8] Despite undetectable insulin levels, their biochemical profiles closely resemble hyperinsulinemic hypoglycemia due to constitutive activation of the insulin signaling cascade. Additional reported features include accelerated linear growth, hemihypertrophy, and polyhydramnios.[4,6] Other features have been variably reported including characteristic facies, acanthosis nigricans, developmental delay and intellectual disability.[5,6]

Given the detrimental neurodevelopmental impact of hypoglycemia in infancy and childhood, achieving euglycemia is critical. Management consists of frequent carbohydrate-rich feedings, often including uncooked cornstarch.[5] However, with this approach, euglycemia is achieved at the expense of excess weight gain and impaired quality of life.[7] Due to the anticipated lifelong duration of treatment, alternate therapeutic approaches are needed. An encouraging option is modified waxy maize heat modified starch (WMHMS) which demonstrates improved tolerability and longer duration of action than uncooked cornstarch.[9]

We report a patient with an activating *AKT2* mutation managed with WMHMS, providing additional insight into the phenotypic spectrum.

Clinical Presentation

The proband is a 4-year-old female born large-for-gestational age at 38 weeks to healthy, non-consanguineous Caucasian parents. She was born via spontaneous vaginal delivery complicated by a 3-minute shoulder dystocia with Apgar scores of 4 at 1 minutes, 7 at 5 minutes and 8 at 10 minutes. Birth weight was 4.14 kg (+2.6 SD), length 56cm (+3.68 SD), and head circumference 36.5 cm (+2.7 SD). Pregnancy was remarkable only for a thickened nuchal fold and bilateral choroid plexus cysts on prenatal ultrasound. Amniocentesis was offered, but ultimately declined.

Shortly after birth, she developed mild hypoglycemia with a lowest documented blood glucose of 2.6 mmol/L. Hypoglycemia was treated with a 10% dextrose infusion for the first 24 hours of life, with a maximal glucose infusion rate (GIR) of 4.2 mg/kg/minute. The presence of bilateral proptosis, periorbital edema, subtle left facial hypertrophy, and central hypotonia prompted evaluation for Beckwit-Wiedemann Syndrome (BWS), which returned negative. Newborn metabolic screen was unremarkable, and microarray demonstrated a normal, female result. The hypoglycemia resolved spontaneously and was not investigated further.

At 6 months of age, she presented with a five-minute, generalised tonic-clonic seizure. At presentation, her blood glucose was 1.9 mmol/L and only transiently responsive to two 10% dextrose boluses. A 10% dextrose infusion was started, and she was admitted to hospital for further treatment and investigation. History was significant for several 1–2-minute episodes of 'staring' and decreased responsiveness occurring in the preceding

two weeks. All episodes occurred in the morning, following periods of fasting overnight. Examination again revealed bilateral proptosis, periorbital edema, and central hypotonia (Figure 1). Auxology demonstrated weight 9.77 kg (+2.1 SD), length 78.3 cm (+5.1 SD), head circumference 46 cm (+2.6 SD).

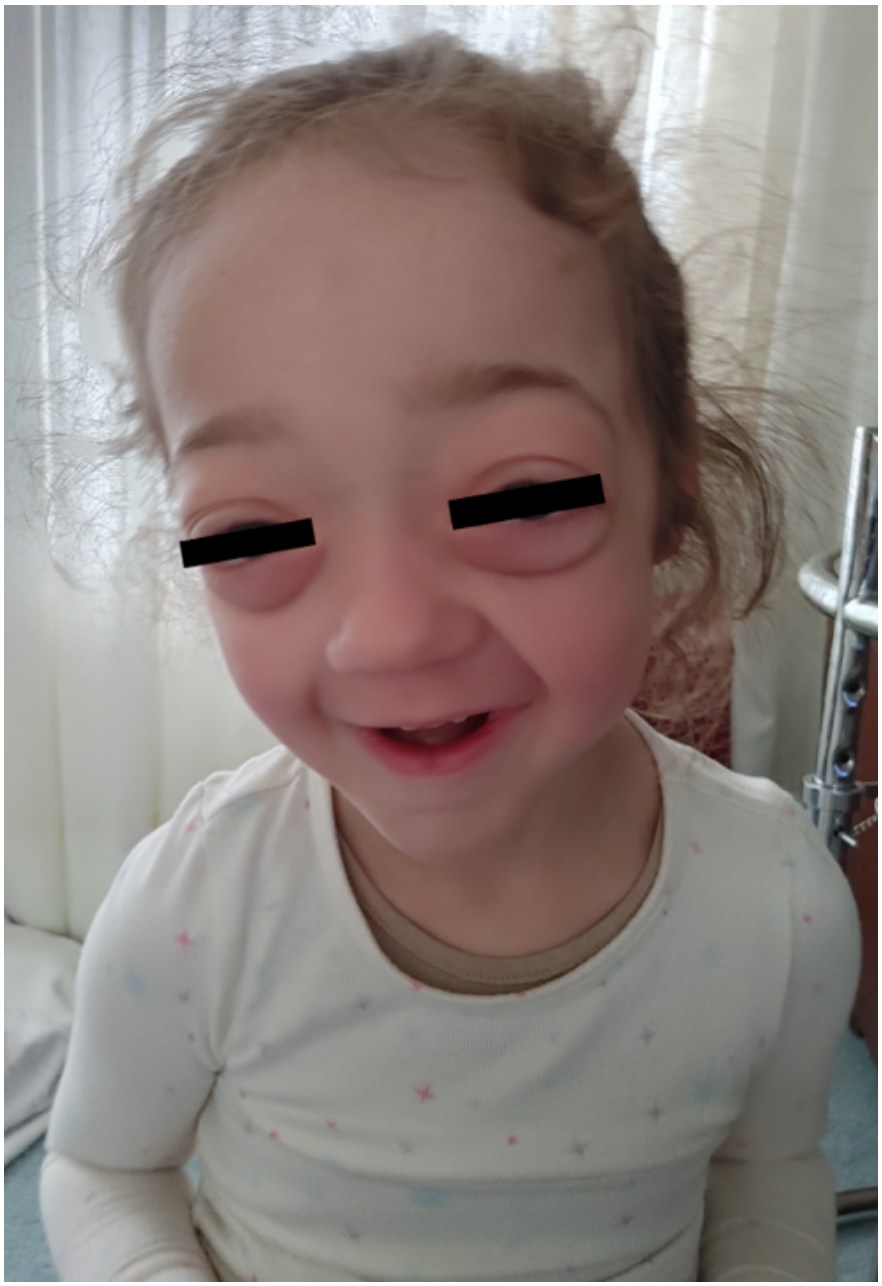

Figure 1: The proband's facial features including bilateral proptosis, periorbital edema, and subtle left facial hemihypertrophy.

During admission, a critical sample was drawn due to ongoing hypoglycemia, which demonstrated hypoketotic hypoglycemia with a laboratory glucose of 1.8 mmol/L and undetectable serum beta-hydroxybutyrate. Cortisol was 207 nmol/L, considered inappropriate in the context of hypoglycemia. To exclude adrenal in-

sufficiency, a standard dose ACTH stimulation test was performed and returned normal. The insulin level, acylcarnitine profile, urine organic acids, and plasma amino acids were not immediately available, as they are processed at an outside laboratory (Table 1).

Table 1: Critical sample at presentation

	Results	Reference Range
Glucose	1.8 mmol/L	3.3-5.5 mmol/L
Serum ketones	<0.1 mmol/L	0.0-0.6 mmol/L
Urine ketones	Negative	——
Serum insulin	<14.4 pmol/L	43.0-194.0 pmol/L
Cortisol	207 nmol/L	133.0-537.0 nmol/L
Growth hormone	6.09 ug/L	0.00-8.00 ug/L
Free fatty acids	227.0 umol/L	100.0-900.0 umol/L
Acylcarnitine	Normal	——-
Plasma amino acids	Normal	——-
Urine organic acids	Normal	——-

A standard dose glucagon challenge was performed immediately following critical sample collection, resulting in an increase in bedside capillary glucose from 1.9 mmol/L to 4.4 mmol/L. This is in keeping with hyperinsulinism, as an increment of at least 1.7 mmol/L suggests suppression of hepatic glycogenolysis by excess insulin.[10] Given this glucagon response and hypoketotic hypoglycemia, a presumptive diagnosis of congenital hyperinsulinism was made. Although not initially available, the serum free fatty acid level returned suppressed at 227 umol/L, further supporting the initial diagnosis.

Initial stabilization was achieved with a bolus of 10% dextrose followed by continuous infusion. Despite GIR exceeding 15 mg/kg/min, she experienced recurrent episodes of hypoglycemia requiring repeated boluses of 10% dextrose. The insulin level subsequently returned undetectable, with no evidence of hemolysis or sample degradation causing an artifactual reduction in measured insulin. Octreotide and diazoxide were separately trialed given her persistent hypoglycemia and biochemical profile otherwise suggestive of hyperinsulinism. She was unable to tolerate a wean of intravenous dextrose or pauses in the infusion exceeding 30 minutes, despite octreotide doses of up to 20 ug/kg/day or diazoxide of 15mg/kg/day. Both medications were eventually discontinued, and she successfully transitioned to continuous nasogastric feeds providing a GIR of 13 mg/kg/min before discharge home.

Given the severity and persistence of hypoglycemia, a comprehensive panel for genes implicated in hypoglycemia, hyperinsulinemia, and ketone metabolism was performed on peripheral blood leukocytes. This demonstrated a pathogenic heterozygous variant in *AKT2*,c.49G>A, p.(Glu17Lys) previously reported in other individuals with gain-of-function *AKT2*variants.[4-8] To assess for possible mosaicism, DNA from skin fibroblasts was subsequently analyzed and found to be positive for the mutation.

Based on the glucose requirements reported in other cases,[7] feeds were changed to three times daily followed by uncooked cornstarch at 1.5-2 g/kg to maintain euglycemia between feeds, in addition to an overnight continuous feed which provided an overall GIR of 4-5 mg/kg/min. More recently, a 4.3 g/kg dose of WMHMS (1.5 packets of Glycosade?, Vitaflo USA, NJ) was trialed in hospital with successful maintenance of overnight euglycemia without the addition of a continuous feed (Figure 2).

Figure 2: Overnight blood glucose following WMHMS administration

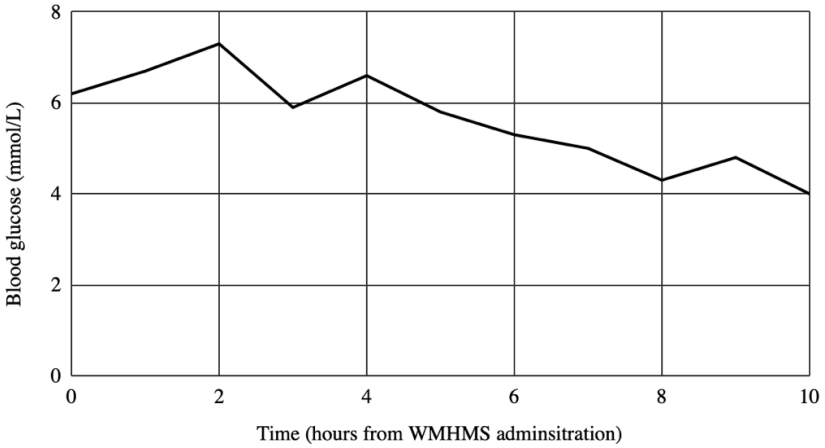

Figure 2: Overnight blood glucose following WMHMS administration.

Currently, at 4 years of age, the hypoglycemia is well-controlled on her current regimen. She continues to exhibit central hypotonia, mild ataxia, and moderate global developmental delay. Owing to these features, a non-contrast brain MRI was performed which demonstrated subtle white matter loss in the parietal region without evidence of cystic change favoured to be sequelae of previous ischemic insult. Investigations for metabolic causes of developmental delay returned negative including serum ammonia, copper, ceruloplasmin, homocysteine, amino acid and acylcarnitine profiles, as well as urine organic acids, oligosaccharides, sialic acid, uric acid, mucopolysaccharide screen, and creatine. In view of the constitutive insulin pathway activation, serial abdominal ultrasounds have been performed for tumour surveillance which have been unremarkable including liver and kidneys normal in size for her age.

Genetic Testing

BWS testing was performed using methylation sensitive, multiplex ligation-dependent probe amplification at the 11p15 locus and Sanger sequencing of *CDKN1C.*

The gene panel for hypoglycemia, hyperinsulinemia, and ketone metabolism is a commercially available panel (Blueprint Genetics, Seattle, WA) and included next-generation sequencing of the following genes: *ABCC8, ACAT1, ACSF3, AGL, AKT2, ALDOA, ALDOB, DIS3L2, ENO3, EPM2A, FBP1, G6PC, GAA, GBE1, GCK, GLUD1, GPC3, GYG1, GYS1, GYS2, HADH, HMGCL, HMGCS2, HNF1A, HNF4A, INSR, KCNJ11, KDM6A, KMT2D, LAMP2, LDHA, MPV17, NHLRC1, NSD1, OXCT1, PC, PCK1, PDX1, PFKM, PGAM2, PGK1, PGM1, PHKA1, PHKA2, PHKB, PHKG2, PIK3CA, PIK3R2, PRKAG2, PRKAG3, PTF1A, PYGL, PYGM, RBCK1, SLC16A1, SLC2A2, SLC37A4* , and *UCP2.*

Discussion

In this case report, we describe a young female with hypoketotic hypoglycemia and dysmorphic features secondary to an activating*AKT2* mutation.

AKT2 is a serine/threonine kinase in the insulin signalling pathway. Insulin activates a transmembrane tyrosine kinase receptor, which phosphorylates insulin receptor substrate (IRS) proteins, leading to activation of phosphadtidylinositol-3-kinase (PI3K).[11]PI3K in turn generates phosphatidylinositol (3,4,5)-trisphosphate which activates AKT.[12] Several AKT isoforms exist, of which AKT2 has been shown to mediate the metabolic actions of insulin.[1] The *AKT2* c.49G>A variant has been reported as *de novo* in patients with a similar clinical picture as our patient (Table 2). This gain of function *AKT2*variant leads to independent, constitutive activation of the insulin pathway in target tissues including liver, adipose, and skeletal muscle.[7] Consequently,

the biochemical profile resembles hyperinsulinism with suppressed free fatty acids and ketones.[13] However, insulin levels are undetectable due to negative feedback from the constitutively active signaling cascade.[14]

Table 2: Summary of the clinical features of individuals with c.49G>A *AKT2* mutations

Clinical features	Our patient	Hussain, et al	Hussain, et al	Hussain, et al	Garg, et al	Arya, et al	Dushar, et al**	Dushar, et al**	Oc Mc al
Sex	F	M_A	M_B	F_c	M	F	M_A	M_B	M
Acanthosis nigricans					X		X_A		
Developmental Delay	X				X		X_A	X_B	X
Dysmorphic features*	X		X_B		X		X_A	X_B	X
Hemihypertrophy	X	X_A		X_C		X	X_A	X_B	
Hypoinsulinemic hypoglycemia	X	X_A	X_B	X_C	X	X	X_A	X_B	X
Hypoglycemic seizures	X	X_A		X_C	X		X_A	X_B	X
Hypotonia	X		X_B				X_A	X_B	
Macrosomia	X	X_A	X_B	X_C	X	X	X_A	X_B	
Polyhydramnios in utero			X_B		X			X_B	

*Facial features = exophthalmos, periorbital puffiness, proptosis, low-set ears, tented mouth, flat nasal bridge.

**The older male proband is designated A and the younger B.

Despite variable clinical features, our patient's presentation overlaps considerably with previous reports, including growth parameters reflective of excess insulin action. The near universal presence of hemihypertrophy is suggestive of mosaicism, which would account for variability amongst other features including acanthosis nigricans, hypotonia, and facial dysmorphisms. Two previously published cases of*AKT2* mutation were found to be mosaic for the variant[7] and notably two siblings inherited the variant from their unaffected father who was found to carry the variant at low level of mosaicism in his sperm.[5] Mosaicism was not detected in our patient's peripheral blood leukocytes or skin fibroblasts, although it cannot be excluded at other tissues.

The variable occurrence of developmental delay is also notable, as this outcome is potentially preventable. Unfortunately, etiologic determination of our patient's developmental delay is confounded by MRI findings consistent with perinatal asphyxia secondary to shoulder dystocia. These abnormalities are unlikely the consequence of her activating *AKT2* mutation, as normal brain MRIs have been documented in five individuals with the same mutation, four of whom have developmental delay or intellectual disability.[4,5,7,8]Nevertheless, hypoglycemia is likely contributory to her delay given her presentation with hypoglycemic seizures and initial challenges obtaining glycemic control. Previous studies of children with congenital hyperinsulinism suggest development is adversely impacted by both hypoglycemic duration and severity, emphasizing the need for prompt recognition and treatment.[15]

At present, the mainstay of treatment is nutritional support with frequent, carbohydrate-rich feeds. Our patient initially required a markedly elevated GIR of 15 mg/kg/min in addition to intermittent dextrose boluses for breakthrough hypoglycemia. Although GIR is reported inconsistently, this exceeds the GIR

of 3-5 mg/kg/min described in three previous cases.[7,8] Current management is nevertheless comparable to other cases, with a GIR of 4-5 mg/kg/min provided by intermittent nasogastric feeds including uncooked cornstarch during the day and a continuous feed overnight.[7] While this approach provides glycemic control, previously described limitations include obesity secondary to excess caloric intake.[7]

The metabolic and quality of life implications of frequent feeding make anti-hypoglycemic agents an attractive therapeutic option. Consistent with previous reports,[5,7] diazoxide and octreotide were ineffective in our patient as these agents target upstream insulin release, as opposed to downstream signaling.[13] Due to its action on this pathway, sirolimus was trialed in a sibling pair with activating *AKT2* mutations. The frequency of hypoglycemic episodes and carbohydrate need were reduced, however overnight fasting was extended only up to four hours.[5] Although no serious adverse effects occurred, use of sirolimus in congenital hyperinsulinism and PIK3CA-related overgrowth spectrum has been associated with severe infectious and hematologic complications, including sepsis and anemia requiring blood transfusion.[16,17] Sirolimus was only modestly effective in children with congenital hyperinsulinism, further highlighting the need for novel therapeutic approaches.[17]

An enticing option is WMHMS, which is approved for children >2 years with glycogen storage disease (GSD) in Canada. WMHMS is a slow-release carbohydrate, shown to provide improved glycemic control with less gastrointestinal discomfort than uncooked cornstarch.[9] Despite its purported benefits, WMHMS did not improve fasting blood glucose compared to uncooked cornstarch in a 6-month-old-male with an activating *AKT2*mutation.[8] However, this result should be interpreted cautiously as expression of pancreatic amylase is substantially reduced in infancy, impairing starch digestion.[18] Age-related differences in digestion could explain the contrasting improvement in fasting tolerance observed in our patient following WMHMS administration. Unfortunately, overnight hypoglycemia necessitated WMHMS discontinuation after three nights at home. Given otherwise unchanged daytime feeds, a conceivable explanation is increased energy expenditure at home, where activity is unrestricted. The family remains willing to use WMHMS and an increased dose of 5.8 g/kg was recommended, though it has yet to be attempted by the family.

Conclusion

We describe the ninth individual presenting with hypoketotic hypoglycemic secondary to an activating *AKT2* mutation causing autonomous activation of the downstream insulin signaling cascade. Our patient's dysmorphic features, developmental delay, and hemihypertrophy provide additional evidence of a broad phenotypic spectrum. Due to the anticipated lifelong duration of treatment, safe and tolerable options are needed. Our initial success with WMHMS indicates it is a promising option, although additional research is needed to establish dosing.

Author Contributions

MP reviewed the literature, authored the manuscript, and briefly participated in the patient's clinical care. DY provides longitudinal clinical care for the patient and was responsible for conceptualization. DY contributed to literature and manuscript review, in addition to editing.

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Conflict of Interest Statement

The authors declare no conflicts of interest.

Consent

In accordance with journal policy, written informed consent was obtained from the patient's parents to publish this report.

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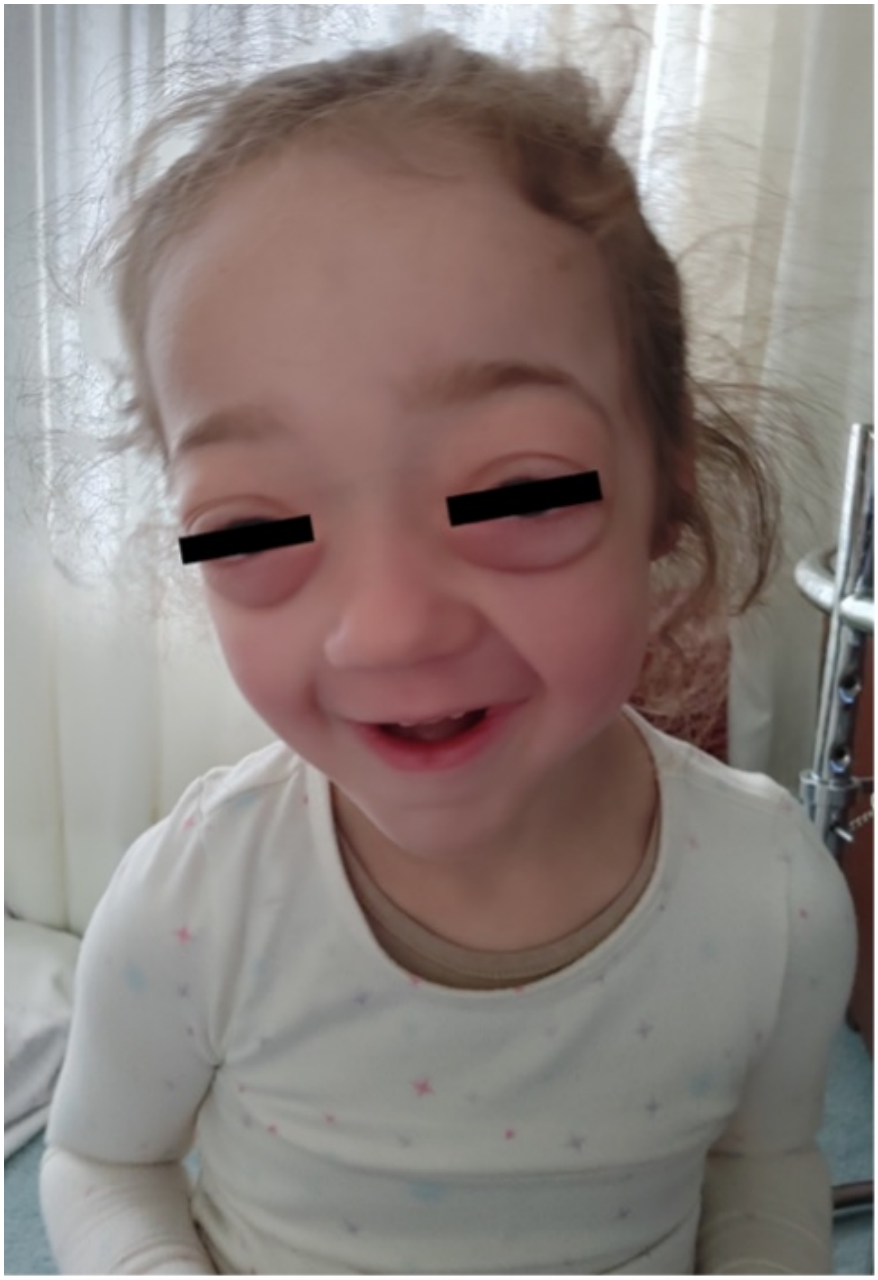

Figure 2: Overnight blood glucose following WMHMS administration