



Ketogenic Diet in Glut 1 Deficiency Through the Life Cycle: Pregnancy to Neonate to Preschooler

Jennifer Kramer, MS, RD¹  and Lisa Smith, MD¹

Abstract

A 19-year-old woman with glucose transporter type 1 deficiency syndrome (Glut1DS) treated with ketogenic diet therapy (KDT) became pregnant. Her pregnancy included close monitoring of her diet as well as the fetus. Shortly after delivery, a lumbar puncture was performed followed by confirmatory genetic test diagnosing the neonate with Glut1DS. The neonate was placed on KDT and has been maintained on diet since infancy. The child is now 5 years of age, asymptomatic, and excelling developmentally. This case presents 2 management challenges, that of a patient with Glut1DS during pregnancy followed by managing a neonate on KDT with minimal guidance available in the literature due to the relative rarity of the condition and this unique situation.

Keywords

ketogenic diet, infantile spasms, nutrition, pediatric, seizures, metabolism, ataxia, dystonia

Received April 6, 2021. Received revised June 15, 2021. Accepted for publication July 2, 2021.

Introduction

Glucose transporter type 1 deficiency syndrome (Glut1DS), also known as De Vivo disease, is a rare genetic disorder resulting in impaired brain metabolism. The Glut1-transporter is the primary receptor responsible for transporting glucose across the blood-brain barrier. Glucose cannot be transported into the brain resulting in a lack of energy for the brain to support both growth and function. A mutation in the SLC2A1 gene is responsible for this and results in varying severity of symptoms.¹ These symptoms most commonly include uncontrolled seizures but also present as deceleration of head growth, global developmental delay, complex movement disorders, and paroxysmal events triggered by exercise, exertion, or fasting.² Glut1DS is a relatively new disease first described in 1991.³ As a result, there has been very little data on the management of Glut1DS during pregnancy, the neonate period, and the first few years of life. The purpose of this is to report on the experience of managing Glut1DS with ketogenic diet therapy (KDT) in an adolescent pregnant female as well as the KDT treatment of her newborn with postnatal diagnosis of Glut1DS at 12 days of life. Glut1DS is treated with KDT and should be initiated as soon as the diagnosis is confirmed.¹ Use of KDT in Glut1DS often dramatically stops seizures and

is effective in reducing severity of the associated movement disorders.⁴

Case Report

A female patient was diagnosed with Glut1DS at 18 years of age after a long history of nonclassic symptoms including migraines and movement abnormalities since 2 years of age. Early developmental language and motor milestones were described as typically occurring at the late end of the normal range, and she has previously been diagnosed with developmental coordination disorder.

She experienced ataxia and dystonia but no seizure activity on multiple electroencephalograms (EEG). Her diagnosis was confirmed with lumbar puncture (cerebrospinal fluid [CSF] glucose 38 mg/dL, serum glucose 101 mg/dL) and subsequent

¹Riley Hospital for Children at Indiana University Health, Indianapolis, IN, USA

Corresponding Author:

Jennifer Kramer, Riley Hospital for Children at Indiana University Health, 705 Riley Hospital Dr, Indianapolis, IN, USA.
Email: jkramer2@iuhealth.org



genetic testing of gene SLC2A1 with nucleotide change c.377G>A and amino acid change p.Arg126His. This mutation has been well described in the literature.⁵⁻⁷ Her neuropsychiatric testing indicated low average intelligence quotient (Full Scale IQ 82). She was started on modified Atkins diet and after several months of diet therapy, her episodes of ataxia, dystonia, and migraines had stopped and her academics had improved. At 19 years of age, she became pregnant and prenatal care began at estimated gestational age of 25 to 28 weeks. Prior to confirmation of pregnancy, she was experiencing increased dystonic movements, headaches, anemia, and low urine ketones despite continued modified Atkins diet. Upon confirmation of pregnancy, her prenatal care was managed by a high-risk obstetrician and included growth ultrasounds every 2 weeks, which were overall normal. The patient also had non-stress tests every 2 weeks and on 2 of those occasions, the infant had pseudo sinusoidal heart rate patterns that resolved after brief monitoring. The patient's care involved genetic counseling; postnatal targeted mutation analysis was elected for infant testing. A mutation typically occurs de novo within a family; however, individuals that are confirmed to be carriers have a 50% risk for recurrence to their offspring in an autosomal dominant inheritance pattern.⁶

Throughout the pregnancy, the patient did experience frequent episodes of abnormal movements. Those events most commonly occurred on days of high anxiety and may have also been related to difficulty maintaining adequate ketosis demonstrated by levels of +1 in urine and beta hydroxybutyrate (BHB) of 0.12 mmol/L. Carnitine level was low and despite supplementation, her carnitine level did not return to normal until after delivery.

Medical team communicated with international expert on Glut1DS, Dr Darryl De Vivo (February 2014), after finding minimal literature to support management of KDT during pregnancy and in newborn phase. It was advised to maintain KDT during pregnancy and use maternal or donor breast milk in the newborn phase for the infant due to the high fat content of breastmilk and for its multiple protective properties.

The female infant was born at term via induced vaginal delivery with Apgar scores of 7 at 1 min and 9 at 3 min, a birth weight of 2.56 kg (5-10%ile, *z*-score -1.46), and a normal head circumference of 33 cm (10-25%ile, *z*-score -0.81). Her initial blood glucose level was 37 mg/dL but after feeding donor breastmilk, her blood glucose levels remained stable. Her physical and neurological exam were both normal; neurologist did advise against the use of phenobarbital if infant began to have seizures since this antiepileptic drug inhibits Glut 1 transport.¹ After a normal hospital course, the infant was discharged home with adoptive parents on day of life 2 on donor breast milk until diagnosis could be determined. Molecular genetic testing was sent for SLC2A1 mutation. At a follow up visit at 12 days of age, a lumbar puncture was performed with CSF glucose positive for hypoglycorrhacia at 28 mg/dL and blood glucose normal at 85 mg/dL with a ratio of 0.32, suggestive of Glut1DS. Glut1DS is considered one of a handful of conditions in which KDT should be used very

early in the course of treatment therefore the infant was admitted to the neonatal intensive care unit and initiated on KDT over the course of 1 week.⁸ She continued to show no evidence of seizures clinically or with EEG monitoring. During this admission, her fat to carbohydrate plus protein ratio was titrated up to a 2:1. She achieved nutritional ketosis with a BHB of 1.31 mmol/L within 48 h of this diet ratio. Since she had a normal EEG pattern and as mother's phenotype was mild, it was determined that a high ratio diet was likely not necessary. This lower ratio was also supported by data from a randomized trial of 38 infants that demonstrated a 2.5:1 ratio diet was as effective as a 4:1 ratio with less side effects.⁹ During diet initiation, the infant was also started on carnitine supplementation at a dose of 25 mg/kg due to a borderline low level of 25 nmol/mL and her mother's known carnitine deficiency. Her diagnosis of Glut1DS was later confirmed by genetic testing of SLC2A1 with nucleotide change c.377G>A and amino acid change p.Arg126His which was the same mutation as her mother. For the first 6 months of life, her feeding plan included a ratio of 2 to 2.5:1 using a combination of Gerber Good Start Gentle (Nestle Healthcare Nutrition) and Ketocal 4:1 powder (Nutricia) at 24 to 27 cal/oz and she was allowed to feed on demand. Her BHB levels were generally <2 mmol/L until 6 months of age and then increased steadily and stayed at 3 to 4 mmol/L despite no overall changes in diet ratio.

From birth to 24 months, her weight trended at 5 to 10%ile weight for age, 2 to 5%ile length for age, weight for length at 25%ile, and head circumference at 25%ile. She struggled with the transition from formula to solid foods. Because diet therapy was the standard treatment for her diagnosis, early intervention with feeding therapy was determined to be in her best interest. She participated in feeding therapy from the age of 18 months to 4 years of age. Now at 5 years of age, she has remained on formula supplementation with a mixture of Ketocal 4:1 powder, Liquigen (Nutricia), and water mixed to a ratio of 5:1. This accounts for an estimated 50% of her energy intake with the remainder coming from solid foods for an overall estimated ratio of 2:1 and 100 kcal/kg/day. The high ratio formula has allowed for a more liberalized intake of carbohydrates and less fat from her solid foods. Her overall energy needs in comparison to standard recommended dietary allowance has consistently been higher. She was referred to nephrology at 18 months of age due to persistent low bicarbonate levels with elevated uric acid and has been treated with sodium citrate. Her developmental progression remains completely normal with no signs of seizure activity or abnormal movements and growth has stayed appropriate for age.

Discussion

In 1991, KDT was introduced as the treatment of choice for Glut1DS.³ Since that time, KDT for Glut1DS has evolved and now includes the use of classic high ratio KDT, supplementation with medium chain triglycerides, modified Atkins diet, and low glycemic index treatment.⁴ For patients on diet

therapy, there is an overwhelmingly positive response for both seizures and abnormal movements. Data from Columbia University as well as results from a global survey through the Glut 1 Deficiency Foundation indicate that patients who begin dietary treatment at a younger age have better outcomes.¹⁰ In a recent report from the International Ketogenic Diet Study Group, 96% of the consensus group advised use of KDT as first line treatment for Glut1DS over triheptanoin even in those that experience abnormal movements and not seizure activity.⁸ This reinforces the need for early diagnosis and intervention including the evaluation of at-risk newborns, infants, and other relatives in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures. Early initiation of the KDT, ideally in infancy, results in better seizure control and improves long-term neurologic outcome. Molecular genetic testing is used to clarify the genetic status of at-risk relatives if the pathogenic variant in the family is known.¹ In Glut1DS, the single most important laboratory observation in Glut1 DS is hypoglycorrachia. All affected individuals reported to date have had CSF glucose values below 60 mg/dL (range: 16.2-52 mg/dL); in more than 90% it is below 40 mg/dL and in ~10% it is 41 to 52 mg/dL.¹ In our case report, both the mother and infant had CSF levels consistent with that of 38 and 28 mg/dL, respectively.

The repeated trend of low carnitine levels in our patient as well as in previous case reports of mothers on KDT indicates necessity to monitor total and free carnitine at onset of pregnancy and intermittently to establish adequate maternal levels in this population. Carnitine is an amino acid used to transport long chain fatty acids into the mitochondria as a substrate for beta-oxidation. Carnitine deficiency can be a result of a rare disorder, primary carnitine deficiency, or related to medications such as the antiepileptic drug valproic acid, malnutrition, hemodialysis, renal tubular dysfunction, or a vegetarian diet.¹¹ It has been documented by Schoderbeck et al¹² that healthy pregnant women may have a decrease in levels of whole blood and plasma carnitine similar to those levels found in patients with carnitine deficiency. The percentage of acylcarnitine on total carnitine in that study was characteristic of secondary carnitine deficiency indicating the need for carnitine supplementation particularly in high-risk pregnancies. There are 2 previous case reports using KDT for epilepsy in pregnancy. While both infants had normal development in their first year of life, one of the infants had bilateral ear malformations of unknown significance.¹³ At 14 weeks gestation, one of the mothers also had carnitine deficiency with low total carnitine of 18.8 mmol/L that responded after 8 weeks of carnitine supplementation of 20 mg/kg. Overall, the safety of KDT during pregnancy is still unknown and needs further investigation. A recent review article brings to question the current recommendation to avoid ketones and carbohydrate restriction in pregnancy and urges this to be further examined as there appears to be a lack of appropriate evidence to continue to support this.¹⁴

Lower levels of ketosis were initially seen in our infant (BHB <2 mmol/L) but did not correlate with any seizure

activity or abnormal movements. At around 6 months of age, those levels increased despite the same level of diet therapy. This may be related to the possibility that fatty acid utilization is very efficient in a neonate thus resulting in lower ketone levels. Previous reports document young children are able to extract and utilize ketone bodies 4 times higher than in adults.¹⁵ There is also evidence that premature infants and/or small for gestational age infants may have less ability to produce ketones due to an immature liver but this does not necessarily mean that they cannot utilize fatty acids as an energy substrate.¹⁶ For many years, use of KDT was discouraged in infancy because of this time of rapid growth and development; however, use of diet in this age is rapidly expanding. In the earliest reports, Nordli et al¹⁷ demonstrated KDT to be effective and safe and showed that infants were able to maintain ketosis. A recent international consensus statement specifically addressed guidelines for application of KDT in infants with refractory epilepsy to provide standardized protocols and management recommendations.¹⁸ The positive outcome for this child supports the use of KDT as early as possible in the treatment of Glut1DS.

Conclusion

Our 2 cases are unique in that they involve management of Glut1DS in a young adult into pregnancy and her infant with Glut1DS. The literature concerning the management of Glut1DS during pregnancy as well as the neonatal period is sparse and it is our hope that our 2 cases will help others in managing this disorder. Owing to the relative rarity of this condition in comparison with intractable epilepsy as well as dietary management being the first line of treatment, more research needs to be directed toward both the efficacy and safety of the KDT during pregnancy as well as in the neonatal period. Questions regarding how aggressive one should be when managing neonates and infants with this condition when one assumes a milder phenotype also needs to be answered. The recent Glut1DS consensus article from Klepper et al discusses that it is unclear if high levels of nutritional ketosis are needed in “milder phenotypes but experience with other genetic diseases” suggests it is still necessary.¹⁹ We were able to achieve ketosis in our neonate and she tolerated the KDT quite well and has remained asymptomatic and developmentally normal. A deceleration in head growth leading to acquired microcephaly is commonly seen in Glut1DS, however this was not the trend seen in our neonate/toddler as a result of appropriate treatment. This case helps validate the concept that very early treatment of the presymptomatic infant is consistent with normal neurological development.

Author Contributions

JK contributed to conception, design, and analysis of information as well as drafting of manuscript with critical revision. LS contributed to conception, analysis of information, and critical revision of article.


Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Jennifer Kramer  <https://orcid.org/0000-0002-2428-7689>

Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

References

1. Wang D, Pascual JM, De Vivo D. Glucose transporter type 1 deficiency syndrome. 2002 Jul 30 [Updated 2018 Mar 1]. In: Adam MP, Ardinger HH, Pagon RA, et al. eds., *GeneReviews*[®] [Internet]. University of Washington, Seattle; 1993–2018:1–21. Available from <https://www.ncbi.nlm.nih.gov/books/NBK1430/>
2. Klepper J. GLUT1 deficiency syndrome in clinical practice. *Epilepsy Res.* 2012;100(3):272-277.
3. De Vivo D, Trifiletti R, Jacobson R, et al. Defective glucose transport across the blood-brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. *N Engl J Med.* 1991;325:703-709.
4. Kass H, Parrish Winesett S, Bessone S, et al. Use of dietary therapies amongst patients with Glut 1 deficiency syndrome. *Seizure.* 2016;35:83-77.
5. Raja M, Kinne R. Mechanistic insights into protein stability and self-aggregation in GLUT1 genetic variants causing GLUT1-deficiency syndrome. *J Membr Biol.* 2020;253:87-99.
6. Brockmann K, Wang D, Korenke CG, et al. Autosomal dominant Glut-1 deficiency syndrome and familial epilepsy. *Ann Neurol.* 2001;50:476-485.
7. Wang D, Kranz-Eble P, De Vivo DC. Mutational analysis of GLUT1 (SLC2A1) in Glut-1 deficiency syndrome. *Hum Mutat.* 2000;16:224-231.
8. Kossoff E, Zupec-Kania B, Auvin S, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: updated recommendations of the international ketogenic diet study group. *Epilepsia Open.* 2018;3:175-192.
9. Raju KN, Gulati S, Kabra M. Efficacy of 4:1 (classic) versus 2.5:1 ketogenic ratio diets in refractory epilepsy in young children: a randomized open labeled study. *Epilepsy Res.* 2011;96(1-2):96-100.
10. Akman C, Yu J, Alter A, et al. Diagnosing glucose transporter 1 deficiency at initial presentation facilitates early treatment. *J Pediatr.* 2016;171:220-226.
11. Bruyn A, Jacquemyn Y, Kinget K, Eyskens F. Carnitine deficiency and pregnancy. *Case Rep in Obstet Gynecol.* 2015; 2015:4, Article ID 101468. <https://doi.org/10.1155/2015/101468>.
12. Schoderbeck M, Auer B, Legenstein E, et al. Pregnancy-related changes of carnitine and acylcarnitine concentrations of plasma and erythrocytes. *J Perinat Med.* 1995;23(6):477-485.
13. Van der Louw E, Williams T, Henry-Barron B, et al. Ketogenic diet therapy for epilepsy during pregnancy: a case series. *Seizure.* 2017;45:198-201.
14. Tanner H, Nitert M, Callaway L, Barret H. Ketones in pregnancy: why is it considered necessary to avoid them and what is the evidence behind their perceived risk? *Diabetes Care.* 2021; 44: 280-289.
15. Wheless J. The ketogenic diet: fa(c)t or fiction. *J Child Neurol.* 1995;10(6):419-423.
16. Ercal B, Crawford P. Ketone body metabolism in the neonate. *Fetal and Neonatal Physiology.* 5th ed. Elsevier; 2017:370–379.
17. Nordli D Jr, Kuroda M, Carroll J, et al. Experience with the ketogenic diet in infants. *Pediatrics.* 2001;108:129-133.
18. Van der Louw E, van den Hurk D, Neal E, et al. Ketogenic diet guidelines for infants with refractory epilepsy. *Eur J Paediatr Neurol.* 2016;20:798-809.
19. Klepper J, Akman C, Armeno M, et al. Glut 1 deficiency syndrome (Glut1DS): state of the art in 2020 and recommendations from the international Glut1DS study group. *Epilepsia Open.* 2020;5: 354-365. <https://doi.org/10.1002/epi4.12414>