Case Report

Positive impact of a modified Atkins diet on cognition, seizures control and abnormal movements in an adult with Glucose Transporter Type 1 Deficiency Syndrome deficiency syndrome

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Abstract: Glucose is the primary energy fuel used by the brain and is transported across the blood-brain barrier (BBB) by the glucose transporter type 1 and 2.[1] A GLUT1 genetic defect is responsible for glucose transporter type 1 deficiency syndrome (GLUT1DS). Patients with GLUT1DS may present with pharmaco-resistant epilepsy, developmental delay, microcephaly, and/or abnormal movements, with tremendous phenotypic variability. Diagnosis is made by the presence of specific clinical features, hypoglycorrhachia and an SLC2A1 gene mutation. Treatment with a ketogenic diet therapy (KDT) is the standard of care as it results in production of ketone bodies which can readily cross the BBB and provide an alternate energy source to the brain in the absence of glucose. KDTs have been shown to reduce seizures and abnormal movements in children diagnosed with GLUT1DS. However, little is known about the impact of KDT on cognitive function, seizures and movement disorders in adults newly diagnosed with GLUT1DS and started on a KDT in adulthood, or the appropriate ketogenic diet therapy to administer. This case report demonstrates the potential benefits of using a modified Atkins diet (MAD), a less restrictive ketogenic diet therapy on cognition, seizure control and motor function in an adult with newly-diagnosed GLUT1SD.

Keywords: GLUT1 deficiency syndrome, modified Atkins diet, cognition, dystonia, dyskinesia, seizure, epilepsy, ketogenic diet, glucose transporter type 1.

1. Introduction

Glucose Transporter Type 1 Deficiency Syndrome (GLUT1DS) is a genetic disorder that impairs glucose transport across the blood-brain barrier. Glucose is the brain’s primary energy source, and its absence may trigger pharmaco-resistant epilepsy, reduced brain growth, developmental delay, and complex movement disorders such as ataxia, dystonia, and paroxysmal exertional dyskinesia.[2] GLUT1DS is an autosomal dominant disorder caused by a mutation in the SLC2A1 gene. The majority of cases are de novo rather than inherited mutations. However, individuals with this disorder can potentially transmit the disease to their offspring. Diagnosis is established by the presence of characteristic phenotypes, hypoglycorrhachia and a mutation in the SLC2A1 gene.

GLUT1DS is considered a spectrum disease. Patients may present with mild symptoms and remain undiagnosed or misdiagnosed with isolated seizure disorders, movement
disorders, or cognitive impairment, while others could develop classic symptoms which lead to a rapid diagnosis. Seizures are the primary presenting symptom of these individuals and typically begin in infancy. Numerous seizure types have been described, including tonic-clonic, myoclonic, absence, and atonic seizures. Interestingly, seizures have been observed to decline or completely resolve when patients reach adulthood without escalation of antiseizure treatment.[3]

Individuals with GLUT1DS also present with abnormal movements including ataxia, dystonia, and hypotonia or spasticity. Movement disorders may be precipitated by exercise and cause difficulty with ambulation. GLUT1DS may also produce cognitive impairment that can range from mild to severe intellectual disability. Language and speech dysfunction is also common. These symptoms may be secondary to abnormalities in the muscles that control production of speech, cortical areas that regulate language, or both. Other described manifestations include unusual eye and head movements beginning in infancy[4], confusion, fatigue, obstructive sleep apnea and headaches.[5]

GLUT1DS currently has no cure and therefore, strategies for providing an alternative energy source to the brain in patients with GLUT1DS are essential. Ketogenic diet therapies (KDT) are high fat, low carbohydrate diets that induce fat metabolism and ketone body production. Data has shown that KDT reduces seizures and abnormal movement in individuals with GLUT1DS but its impact on cognition remains unclear.[4] The classic ketogenic diet is strict with regard to precisely weighing proportions of foods using a gram scale and maintaining a consistent ratio of fat to carbohydrate and protein throughout the day as well as total calories consumed. It is therefore difficult to follow for some individuals and in particular, adolescent and adult patients. The modified Atkins diet (MAD), a less strict KDT and frequently used in adults with chronic epilepsy[6], may be an option but little is known about its benefits in adults with GLUT1DS, potential long-term side effects given that ketogenic diet therapy may be life-long, and risks of teratogenicity in pregnancy.[7] We present a case of a patient diagnosed with GLUT1DS as an adult who, following the initiation of MAD, not only demonstrated improvement in the frequency and severity of abnormal movements and seizures but also displayed significant improvement in cognitive function resulting in independence in performing activities of daily living (ADLs), which was not possible prior to starting a KDT.

2. Case Report

The patient was born full-term by vaginal delivery following an uncomplicated pregnancy. Family history was negative for genetic disorders and consanguinity. Her early development was normal until age ten months, when she developed mild language regression followed by an afebrile generalized tonic-clonic seizure. She was admitted to a local hospital and underwent a lumbar puncture, CT scan of the head, brain MRI and EEG. Initial diagnostic evaluations were unrevealing except for hypoglycorrachia with CSF glucose levels of 40 mg/dl and 33 mg/dl five years later. Because the etiology remained
unclear, no treatments were started initially. She continued to demonstrate slowed progression in cognitive, language, and motor skills. She walked with assistance at age two years, independently at age four years, and spoke in two-word sentences at four or five years.

At nineteen months, she experienced episodes described by her parents as a “drunk” appearance, with sweaty palms, difficulty walking, and dystonic movements with right arm and leg inversion or extension, neck contraction, and head rotation followed by rhythmic, circular oscillating movements of the head. These events appeared to improve over several hours and could be triggered by exercise and long car rides. She was treated with several antiseizure medications based on the assumption that these events were seizures. Around this time, the patient also developed absence seizures with brief staring and rolling movements of her tongue for 15 seconds approximately 20 times per day. She also continued to have rare tonic-clonic seizures which were controlled during infancy, but absence seizures, dystonic episodes, language impairment, and severe intellectual disability persisted into adulthood.

At the age of 21 years, the patient was referred for a neurocognitive assessment. During the Wechsler Adult Intelligence Scale-IV (WAIS-IV), she did not comprehend task instructions and was instead assessed with the Differential Ability Scales (DAS-II) that she completed. Her score on this assessment, analogous to an intelligence quotient (IQ) score, was 37, which rated her intellectual disability into the moderate to severely impaired category. Her academic skills were also assessed through the Wechsler Individual Achievement Test II (WIAT-II). She performed at the pre-kindergarten level in reading and math problem-solving skills. Regarding her adaptative functioning skills, she was identified as having strengths in social and community skills, rating her social interaction and language expression between four and six years of age, but significant weaknesses in motor skills, and overall personal living skills.

The patient ultimately underwent genetic evaluation at age 22 years and the analysis demonstrated a missense mutation in the SER313TYR in exon 7 of the GLUT1 gene, which was consistent with a diagnosis of Glucose Transporter Type 1 Deficiency Syndrome (GLUT1DS). Her seizures subsided by age 24 years with levetiracetam and zonisamide. The patient’s family attended an educational symposium on GLUT1DS and learned that the standard of care in management is ketogenic diet therapy. She saw an adult neurologist at age 25 years who recommended a modified Atkins diet where she restricted carbohydrates to 30 grams of net (subtracting fiber) carbohydrates per day. She did not initially measure urine ketones or adhere strictly to the diet. She was seen in the Johns Hopkins Adult Epilepsy Diet Center at age 27 years and instructed to measured urine ketones and reduce carbohydrates to fewer than 20 net grams per day. Urine ketones were initially in the moderate range. At the time of the initial visit, she was on lioresal for spasticity, seizure-free on acetazolamide and had previously tried felbamate, phenobarbital, phenytoin, topiramate, valproate, carbamazepine, levetiracetam,
zonisamide, and lacosamide. Her dystonic episodes decreased significantly from daily spells to one every one or two months and were typically associated with over-exertion, increased carbohydrate intake, or catamenial pattern. Regarding her seizures, she tapered off acetazolamid and remained on MAD monotherapy without recurrence of seizures. She was placed on Triheptanoin for a brief period of time, but this therapy was not well tolerated and then stopped.

Her cognition has improved over the course of years on the diet. At the age of 31 years, she underwent a second neuropsychological evaluation. This time, she was able to understand instructions for the WAIS-IV, and completed the perceptual reasoning and verbal comprehension domains. Her overall score was 52, which classified her in the mild to moderate range of intellectual disability. Her academic achievements were tested again with the WIAT-III, where she remained able to read at a below first-grade level. Her spelling score also improved with minimal improvement in math problem-solving. Regarding her adaptive functioning skills, her social/communication skills improved from those of a four and a half-year-old girl to a five year and two-month-old; personal living skills improved from age three and five months to ten and three months; however, community living declined from age five and four months to four and nine months. Currently, she is able to express her feelings, speak in complete sentences, take videos with her iPad, and watch TV using the remote control. Family can provide justification for reasons for behavior modification which was not previously possible. In addition, she now performs activities of daily living unassisted such as taking showers, and the family is planning to engage her in reading lessons with the assistance of ongoing occupational therapy.

### Table 1. Neuropsychological evaluations

|                                | Age 22 | Age 31 |
|--------------------------------|--------|--------|
| **Intelligence quotient**      | 37*    | 52**   |
| **Intellectual disability severity** | Severe – moderate | Mild – moderate |
| **Academic skills**            |        |        |
| Word Reading                   | <1+    | <1**   |
| Spelling                       | Pre-Kindergarten | Kindergarten |
| Math Problem Solving           | Pre-Kindergarten | Pre-Kindergarten |
| **Adaptive functioning skills**|        |        |
| Social/communication           | 4 1/2¥ | 5 1/6¥ |
| Personal living                | 3 5/12 | 10 1/4 |
| Community living               | 5 1/3  | 4 3/4  |

* Differential Ability Scales (DAS-II) score
** Wechsler Adult Intelligence Scale-IV (WAIS-IV) score
+ Wechsler Individual Achievement Test II
++ Wechsler Individual Achievement Test III
¥ Scales of independent behavior – Revise scale (years of age)
¥¥ Adaptive behavior Diagnostic scale (years of age)
As part of the standard of care, her fasting lipid profile was monitored prior to the beginning of the diet and at least once every year. This patient has been treated with MAD for seven years and her lipid profile has remained stable over time (Figure 1) as well as selenium, zinc, vitamin D, free and total carnitine levels. To monitor bone health, a bone density scan is recommended at baseline if risk factors are present (individuals who are post-menopausal, using certain antiseizure medications [e.g. valproate, phenytoin, carbamazepine, phenobarbital], non-weight bearing, those with a history of fractures, chronic use of corticosteroids, or vitamin D deficiency) and every five years if the patient remains on the diet, or sooner if the results are abnormal. This patient underwent a bone density scan after 5 years on MAD which was within the expected range for age. She experienced no other reported side effects.

![Figure 1. Fasting lipid profile of a patient with GLUT1 deficiency syndrome treated with a modified Atkins diet.](image)

3. Discussion

Since GLUT1DS was first reported in 1991[9], little has been described about the benefits of using a ketogenic diet therapy (KDT) in adults with GLUT1DS and its long-term side effects on the cardiovascular system, bone health, and teratogenicity effect in women of childbearing potential. This case report highlights the favorable impact of KDT on cognitive function, seizure control, and reduction in abnormal movements in an adult newly diagnosed with GLUT1DS, the effectiveness of a modified Atkins diet (MAD) as an alternative to the classic KD, and its favorable safety profile.

Ketogenic diet therapies are considered first-line for GLUT1DS as they provide an alternative energy source to the brain in the form of ketone bodies.[4] When the diagnosis is confirmed in infancy, the therapy should be implemented as early as possible to ensure brain development and mitigate long-term sequelae. However, the significant phenotypic variability of the disorder results in diagnosis and treatment delays[5] which may explain why our patient remained undiagnosed until the age of 22 years. There are a variety of KDTs that can be considered for this disorder. The classic KD provides a higher ratio of fat to carbohydrate and protein combined compared to more liberal, modified diets, producing higher concentrations of ketone bodies, and is typically chosen for children.
Alternatively, MAD may be preferred in adults and adolescents as a more liberal option than the classic KD which may result in higher adherence rates. In the patient presented here, she was already experiencing difficulty limiting carbohydrates to fewer than 30 grams of net carbohydrates daily when first seen in the Adult Epilepsy Diet Center, and a much stricter diet may not have been feasible. The low glycemic index treatment (LGIT) which has been shown effective in pharmacologic resistant seizure disorders such as Angelman syndrome[10], but may not produce adequate ketone levels for patients with GLUT1DS and therefore, it is not recommended in GLUT1DS.[11,12] Given the age of our patient at the time of diagnosis, she was initiated on MAD.

The patient had seizure resolution in early adulthood without recurrence after tapering antiseizure drugs, and she has remained on diet monotherapy since then. Decreased seizure frequency and severity as well as seizure control following the introduction of KDT has been documented.[13] A survey study demonstrated more than 90% seizure reduction in over 80% of participants following diet initiation.[14] Seizure-free rates were similar between the classic KD and MAD, supporting the use of MAD as an efficacious alternative in GLUT1DS. Notably, studies also support the introduction of the diet in adulthood as these individuals seem to benefit from therapy.[15] Other therapeutic options should be considered if patients have little to no response to diet therapy, suffer from severe side effects (substantial abdominal pain, diarrhea, constipation, nausea), or are unable to produce ketones.[16] Our patient was initially treated with triheptanoin[17] along with MAD, but this was later stopped due to worsening obsessive-compulsive behaviors.

Movement disorders are the second most common manifestation of GLUT1DS after seizures.[18,19] Paroxysmal eye-head movements are characteristic in infancy, while motor disturbance events such as ataxia, paralysis and involuntary movements develop later in life. Other movement abnormalities include dystonia, spasticity, chorea and tremors. Ketogenic diet therapy has been effective in reducing movement abnormalities in pediatric patients with GLUT1DS. A retrospective cohort study that included 18 pediatric patients showed improvement of abnormal movement in 80% of patients after the implementation of a ketogenic diet.[20] Our patient had daily dystonic episodes since childhood and, even despite her late diagnosis and treatment, the frequency of her spells significantly decreased from daily to every one or two months when she started MAD. Her occasional episodes were precipitated by increased carbohydrate intake, long car rides, and exercise.

Regarding cognitive function in GLUT1DS, reports have described a broad spectrum of cognitive dysfunction that ranges from mild to severe intellectual disability and frequently correlates with disease severity.[21,22] Dysarthria and language impairment are present in almost all individuals. Deficiencies in visuospatial and visuomotor abilities are also prevalent in these patients.[19,23] The efficacy of KDT on improving cognitive function has been poorly studied and data in adults is almost nonexistent. A recently published retrospective study of 25 patients with GLUT1DS suggested that KDT seems to
considerably improve the overall cognitive performance of patients with GLUT1DS. This same study showed that the delay in diet initiation might have a negative impact on cognitive outcomes.[24] But the remaining question was whether the introduction of KDT in an adult newly diagnosed with GLUT1DS would have an effect on cognitive outcomes. The initial goal in this patient was to prevent further cognitive decline, although improvement was not anticipated given her age and long-standing disease. However, neuropsychological assessment revealed significant improvement in her intellectual functioning from severe-moderate to mild-moderate range of intellectual disability (reliable change index (RCI) > 1.96, p <0.05). Her personal living skills (i.e., self-care, domestic skills) improved from those of a three-year-old to a ten-year-old. Improvements were also appreciated in her spelling, mathematics, social skills, and communication while there was a slight decline in community living skills. She can now perform activities of daily living independently including showering, speaking in complete sentences, understand instructions from her parents and caregivers, and will soon be engaged in reading lessons. None of these activities were possible prior to the introduction of KDT.

The adverse effects of KDT are common but easy to manage. Nephrolithiasis[25–27], dyslipidemia[28], gastrointestinal side effects[26], weight loss, and amenorrhea[6] are among the most frequent side effects of the diet. Dyslipidemia and cardiovascular risks are of concern, particularly for those patients who require long-term diet therapy.[29] In a prospective study of 31 adults with epilepsy treated with MAD, participants showed a significant increase in markers of cardiovascular health at 3 months following the introduction of the diet, but most of these markers decreased at 6 months, suggesting a compensatory adaptation of the body to the diet.[30] Another critical side effect of KDT is osteoporosis and osteopenia. A longitudinal study of 25 children with intractable epilepsy treated with KDT showed a sharp decline in bone health status over a period of 15 months.[31] Careful monitoring of bone health is essential to prevent fractures in these individuals. Of note, our patient has maintained a stable lipid profile over the past 7 years without signs of dyslipidemia and she has never reported diet associated adverse effects. She also takes vitamin D3 and calcium supplements to maintain her bone health and exercises regularly while treated with the diet.

4. Conclusions

This case report demonstrates the efficacy of MAD in the treatment of an adult newly diagnosed with GLUT1DS and its significant effect on cognitive function, maintained seizure control, reduction in movement disorder symptoms and ultimately, improvement in quality of life. Ketogenic diet therapies have a favorable safety profile and can be used life-long. Bone health and lipid profiles should be closely monitored to prevent fractures and cardiovascular events in the long term.

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reviewed the manuscript. M.C.C. conceptualized the project, edited and prepared the final version of the manuscript.

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