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Use of dietary therapies amongst patients with GLUT1 deficiency syndrome

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ABSTRACT

Purpose: GLUT-1 deficiency syndrome (GLUT1DS) is a neurologic disorder manifesting as epilepsy, abnormal movements, and cognitive delay. The currently accepted treatment of choice is the classic 4:1 ratio ketogenic diet.
Methods: A 2-page survey was distributed to all attendees of a family-centered conference for GLUT1DS in July 2015. The surveys were completed by parents, collected anonymously, and information analyzed in a database.
Results: Surveys were received from 92 families, of which 90 (98%) had been treated with dietary therapies. Diets used were extremely varied: 59 were treated with the classic ketogenic diet (KD), 29 with the Modified Atkins Diet (MAD), 4 with the Medium-chain Triglyceride (MCT) Diet and 2 with the low glycemic index treatment. The mean diet duration was 5.5 years (range: 1 month–20 years). Of those with seizures, 95% of the children had >50% seizure reduction and 80% had >90% seizure reduction. Children who were seizure-free were currently younger on average (8.2 vs. 11.6 years, $p = 0.01$) and slightly younger at GLUT1DS diagnosis (3.8 vs. 5.3 years, $p = 0.05$). There was an equal percentage of children seizure-free receiving the KD/MCT Diets compared to the MAD/Low Glycemic Index Treatment (74% vs. 63%, $p = 0.30$). The majority (64%) were not receiving anticonvulsants.
Conclusion: This represents the largest series of KD experience in children with GLUT1DS. Nearly all patients surveyed were on dietary therapies for long durations with reported excellent seizure control, often without anticonvulsant drugs. Several different ketogenic diets were utilized with similar efficacy. Early diagnosis and treatment were correlated with success.

1. Introduction

Glucose-transporter 1 deficiency syndrome (GLUT1DS) is a metabolic disorder resulting from a dominant mutation of the solute carrier family 2, facilitated glucose transporter member 1 (SLC2A1) gene [1,2]. The result of this haploinsufficiency is decreased brain glucose accumulation and resultant encephalopathy. Clinical manifestations of this disorder are variable but often include seizures, movement disorders, and cognitive impairments [2–6].

The current gold standard treatment for GLUT1DS is the classic ketogenic diet (KD) [2–7]. The KD is a high fat, adequate protein, low carbohydrate diet in continuous use since 1921 for the treatment of refractory epilepsy [8]. In an effort to improve diet tolerance, the modified atkins diet (MAD), which limits the amount of carbohydrates consumed to 10–20 g per day, was introduced as an alternative to the classic KD in 2003 [9]. Both dietary therapies are helpful in approximately 50% of children who implement them, and recent evidence also suggests they may be similarly effective in adults [8,9]. Long-term adverse effects include hypercholesterolemia, growth disturbance, acidosis, and kidney stones [8].

Since the first reports of GLUT1DS in 1991 [1], the classic KD has been consistently described as the primary adjunctive modality for treatment of the underlying disorder and its symptomatology [2–7]. Recognizing that the KD has long-term side effects, especially relevant for a population that may require it for many years, alternative treatments have been studied. These include the

Abbreviations: GLUT1DS, Glucose-1 transporter deficiency syndrome; MAD, modified atkins diet; KD, ketogenic diet; LGIT, low glycemic index treatment; MCT, medium chain triglyceride.

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MAD [10–13], ketone esters [14], triheptanoin [15], alpha lipoic acid [16], and acetazolamide [17].

Until 2012, only mostly small series of 1–10 patients using dietary therapies had been reported [7,18]. A single-center study from Columbia University in 2012 described the responses to the KD in 64 children; 61 of whom had active epilepsy [2]. A large majority (41/61, 67%) were seizure-free with the KD, mostly within 1 month of treatment [2].

Although recommendations by several GLUT1DS centers have been made to use the classic high 4:1 ratio (fat: carbohydrate and protein grams) KD and check serum ketosis [2], in our anecdotal experience and personal communications with many GLUT1DS families, this is not universally followed. The use of alternative diets appeared widespread, value of ketosis questioned, and duration of dietary therapy variable. The GLUT1 Deficiency Foundation leadership reported many unanswered questions from parents about optimal dietary therapy management.

2. Methods

A two-page, 21-question survey was created with the assistance and guidance of the GLUT1 Deficiency Foundation (Supplemental material). Questions included basic demographics of the child (age of GLUT1DS diagnosis, current age, gender), diet currently receiving, diet duration, seizure and other neurological manifestation outcome, adverse effects, and other anticonvulsants. Although the survey was primarily focused on dietary therapies for epilepsy, parents were asked to fill out as much as they could even if their child had never been treated with a therapeutic diet. No questions were specifically asked about GLUT1 genetic diagnosis, baseline seizure type or frequency, or EEG findings. Parents were asked to circle the current diet (and ketogenic ratio) they were on, and if they had switched between diets, but other specific details of ratio changes, carbohydrate limit, or calorie adjustments over the years were not asked in this survey.

Surveys were distributed and then collected anonymously at the July 2015 GLUT1 Deficiency Foundation biannual parent conference held in Orlando, Florida. Those returning a survey were given a gift card for their participation. One week after this meeting, electronic versions of the survey were emailed to families not in attendance of this meeting by Ms. Glenna Steele (GLUT1 Deficiency Foundation, USA) and Ms. Emma Williams (Matthews Friends Charity, United Kingdom). These families were from countries including primarily United States, United Kingdom, Italy, Germany, Australia and Japan according to the GLUT1 Deficiency Foundation leadership. Survey information was entered into a database and analyzed. No surveys were accepted 1 month after the GLUT1 Deficiency Foundation conference.

This survey and research received approval from the Johns Hopkins University Institutional Review Board. Implied consent was granted by the survey-based nature of this research. Categorical data were analyzed using Chi square analysis without continuity correction. Comparisons of means were analyzed using a two-tailed *t*-test. The significance level for all tests was $p < 0.05$.

3. Results

3.1. Overall demographics

Ninety-two families completed the 2-page survey and returned them for analysis. The majority (51, 55%) completed the survey at the GLUT1 Deficiency Foundation meeting, with the remainder emailing or faxing their surveys afterwards. Surveys were collected over a 1 month period. Of these surveys, two families reported never having been on dietary therapy due to inclusion in C7 oil (triheptanoin) trials [15], they were excluded from further analysis. No other family filled out the survey stating that they had not been on dietary therapy.

There was a large range of subjects included, with a current age of 1–24 years (mean 9.9 years, median 9 years). GLUT1DS was also diagnosed at various ages, ranging from 0.1 to 18 years (mean 4.8 years, median 4.0 years). The youngest patient was 1 month at diagnosis. Forty-seven (52%) were female. There was no difference in demographics between the patients completing the survey at the Orlando meeting compared to those who completed it afterwards.

3.2. Variety of dietary therapies used

Similar to the wide range of subjects, there was an equally variable list of dietary therapies used by these patients. Families were asked which diet the patient was currently receiving (or had just been discontinued if no longer on dietary therapy). The classic ketogenic diet was being used by 59, with the MAD used by 29 [9], MCT (medium chain triglyceride) ketogenic diet by four [19], and the LGIT (low glycemic index treatment) by two [20]. For those subjects receiving the KD, the ratios were also variable when reported: 4:1 ($n = 16$), 3.5:1 ($n = 2$), 3:1 ($n = 20$), 2.5:1 ($n = 1$), 2:1 ($n = 13$), and 1.5:1 ($n = 2$). Seventy-eight patients were on the KD at some point, of which one family did not answer regarding fasting and admitting during initiation. Of the remainder, 37 (48%) were fasted at KD onset and 70 (91%) were admitted to the hospital.

The mean age of diet onset was 4.8 years (SD = 3.87; range: 0.1–18.5 years), with most families reporting starting the diet within months of the diagnosis of GLUT1DS. Nine patients were already on dietary therapy when the GLUT1DS diagnosis was made. Children were started on the KD at a slightly younger age than those initiated with the MAD or LGIT, 4.1 (SD 3.1) vs. 5.9 (SD = 4.9) years ($p = 0.08$).

Switching between dietary therapies was common, with altogether 24 (27%) changing between the KD, MAD and LGIT. Thirty-three (37%) reported that a discussion occurred between their family and the neurologist about transitioning from the KD to the MAD or LGIT, of which 21/33 (64%) in fact made that change. In fact, of the 31 patients currently on the MAD or LGIT, 19 originally started with the KD. Five switched from the MAD to the KD, including three who had originally started with the KD.

3.3. Seizure outcomes

Nine patients were being treated with dietary therapy for abnormal movements or cognition and did not have epilepsy. Of the remainder ($n = 82$), outcomes were excellent with 38 (46%) reporting seizure freedom, 28 (34%) with 90–99% seizure reduction, 12 (15%) with 50–89% seizure reduction, and only 4 (5%) with <50% improvement. Altogether, 95% of the children had >50% seizure reduction and 80% had >90% seizure reduction, which is significantly higher than most patients with epilepsy treated with ketogenic diets in the literature [8]. Of the four children with <50% seizure reduction, two are currently off therapy. Two patients had improved movements and one had improved cognition despite lack of seizure control.

Data was analyzed to determine if any factors led to a higher likelihood of seizure freedom in this population (Table 1). Children who were seizure-free were currently younger on average (8.2 (SD = 5.7) vs. 11.6 (SD = 5.2) years, $p = 0.01$) and slightly younger at diagnosis of GLUT1DS (3.8 (SD = 3.5) vs. 5.3 (SD = 3.4) years, $p = 0.05$). In addition, they were less likely to be on anticonvulsant drugs (13% vs. 57%, $p < 0.001$), which likely reflects neurologist practice of continuing medications if seizures persisted.

Perhaps most compelling was the lack of any significant difference in outcomes with different diet variants. There was an

Table 1
Factors correlated with presence of reported seizure freedom.

Factor	Presence (n = 38)	Absence (n = 46)	p value
Mean age at GLUT1 diagnosis (years), (SD)	3.8 (3.5)	5.3 (3.4)	0.05
Mean age at diet onset (years), (SD)	4.0 (3.6)	5.0 (3.5)	0.22
Mean current age (years), (SD)	8.2 (5.7)	11.6 (5.2)	0.01
KD/MCT currently	28 (74%)	29 (63%)	0.30
4:1 KD	5 (13%)	11 (24%)	0.21
Checking blood ketones	22 (58%)	25 (54%)	0.74
Fasted at diet onset	17 (45%)	20 (43%)	0.91
Gender (female)	19 (50%)	23 (50%)	1.00
On anticonvulsants?	5 (13%)	26 (57%)	<0.001
Survey collected at GLUT1DF meeting?	19 (50%)	24 (52%)	0.84
On carnitine?	23 (61%)	25 (54%)	0.57

equal percentage of children seizure-free receiving the KD or MCT diets when compared to those on the MAD or LGIT (74% vs. 63%, p = 0.30). Additionally, for those receiving the KD, there was no difference between those on a 4:1 (strictest) ratio and those with lower ratios. Five of 16 (31%) on 4:1 ketogenic ratios when using the KD were seizure-free compared to 21 of 38 (55%) on lower ketogenic ratios, p = 0.11.

3.4. Antiseizure drugs and supplements

The minority of patients were currently receiving anticonvulsants, with only 32 (36%) reporting the use of drugs in combination with dietary management. A wide variety of anticonvulsants were used with the most common being levetiracetam (n = 8), acetazolamide (n = 6), lamotrigine (n = 6), ethosuximide (n = 4), and clonazepam (n = 3). Only one child was receiving valproate (90–99% seizure reduction) and none were treated with phenobarbital, both theoretic GLUT1 inhibitors [21,22]. Specific information about benefits of any particular anticonvulsant was not questioned in this survey.

All families on dietary therapy were appropriately receiving a daily multivitamin and calcium. However, 79% were on extra supplementation beyond that which is advocated by ketogenic diet experts for routine use [23]. The most common was carnitine [24], which was used by 52 families, followed by oral citrates in 25 [25]. Additional MCT oil was given by 20 families and several also wrote in "extra oils".

3.5. Other diet benefits

Recognizing that many families have reported benefits in the abnormal movements and cognitive dysfunction in GLUT1DS by using dietary therapy, the survey asked about potential benefits for abnormal movements specifically. Seventy-six described having abnormal movements and all reported benefit. Sixty-four (84%) agreed that the benefits were "much better" with the remainder (n = 12) stating they were "slightly better".

3.6. Ketones

Parents were queried regarding their personal practice with checking for ketosis while on dietary therapy. Thirty-one (34%) routinely checked blood ketones with home fingerstick devices, 31 (34%) only checked urine acetoacetate using ketone strips. Nineteen (21%) reported documenting both blood and urine ketones while the minority (9, 11%) checked neither. Altogether, 50/90 (56%) periodically checked blood ketones, which is not a universal recommendation of ketogenic diet guidelines but has been advocated by some centers for GLUT1DS [2,23].

Parents generally believed there was a correlation between ketones and neurologic function. Twenty-four families did not have active seizures, so were unable to assess this correlation, but in the remainder with at least periodic seizures, 44/66 (67%) reported a correlation between seizures and the level of ketosis, 7 (11%) saw no correlation, and 15 (23%) were unsure. There was no increased likelihood of seizure freedom in those who checked blood ketones compared to those who did not, 58% vs. 54%, p = 0.74. Interestingly, the perceived correlation between seizures and other neurologic manifestations (stated as "abnormal movements/learning/behavior") was even stronger, with 65/90 (72%) reporting a correlation, 7 (8%) without correlation, and 18 (20%) unsure.

3.7. Puberty

Twenty-two children were reported as undergoing puberty while receiving dietary therapy in this cohort. Fourteen (64%) had a reported "change" in seizure frequency, although the survey did not specify if seizures improved or worsened. The remainder had either no change in seizures or the family was unsure. Eleven (50%) had a decrease in ketosis level during this transition into adolescence.

3.8. Diet discontinuation

The total duration of dietary therapy in this population was significantly longer overall than the traditional 2 years recommended by most experts [23]. The mean diet duration was 5.6 years (SD = 4.5; range: 1 month–20 years). Three children were no longer on dietary therapy, current age range 4–17 years.

Parents were asked if their neurologist had ever discussed with them the possibility of ever discontinuing dietary therapy altogether in the future. Twenty-one (23%) recalled that conversation, but more (37%) were told the opposite, that dietary therapy was a lifelong treatment for GLUT1DS. Thirty-six (40%) did not recall such a discussion. When queried about their personal beliefs, eight (9%) planned to come off the diet (including the three who did), 22 (24%) had no plans to ever discontinue dietary therapy, and the majority (60, 67%) were unsure about eventually stopping their child's diet.

3.9. Side effects

Parents were asked to write in any adverse effects that occurred during their child's time on dietary therapy. Fifty-nine (66%) reported difficulties but none stated this was a reason for discontinuation (and as stated previously, only three have discontinued the diet for inefficacy). Most of these side effects were gastrointestinal system related, including constipation (n = 24), weight loss or hunger (n = 6), and gastroesophageal reflux (n = 5). Only two children had kidney stones, two had reported acidosis, and one with elevated serum cholesterol levels. Several parents commented on the diet being restrictive or difficult to adhere to. Many shared personal tips for improving compliance with dietary therapy over many years.

4. Discussion

While it may be impossible to know the exact percentage of GLUT1DS patients who are receiving dietary therapy, we believe that we have reached a significant number of patients with the help of the GLUT1DS Foundation and the use of email and various social media platforms. Only two out of the 92 respondents

reported having never been on any form of dietary therapy, only due to triheptanoin use. Because this survey focused mainly on dietary therapy, some families not on dietary therapy may have chosen not to respond, yet we believe this suggests the vast majority are on diets.

Of those that responded and are receiving dietary treatments, there was an overwhelmingly positive response for control of both seizures and abnormal movements. The majority of patients were able to achieve this success without the use of anticonvulsants and sustain this level of control for many years. These results from multiple patients worldwide is similar to the single-center results from Columbia University, with the majority achieving >90% seizure reduction and many off anticonvulsant drugs [2].

Those who began dietary treatment at a younger age had better outcomes overall. Those who had an earlier diagnosis also tended to achieve better results than their older counterparts. This powerful finding confirms previous hypotheses about GLUT1 treatment and suggests that early detection and rapid implementation of dietary therapy may be important in the treatment of GLUT1DS [2,7,13]. Genetic screening for the SLC2A1 gene has helped expedite the earlier diagnosis of GLUT1DS and may lead to sooner dietary interventions [5,7]. Additionally, recognition of early onset absence epilepsy [26] and other movement disorders as features of GLUT1DS may also lead to earlier detection. While alternative treatments, such as the use of triheptanoin, are under clinical investigation, we feel strongly that implementation of dietary therapy should not be delayed after a diagnosis has been made [15,27].

Although these results and other studies have established dietary therapy as the gold standard of treatment, the specific diet that one should use is not as clear. As we suspected, diets used by families varied widely. Many families were using alternative diets such as the MAD and the LGIT. Even among those using the classic KD, ratios varied widely and ranged from 4:1 to 2:1 and included the MCT diet. Outcomes reported were nearly identical among all diets and ratios. We were surprised that a slight trend towards improved seizure-free rates were seen in those NOT on a 4:1, but this may still reflect the modest sample size in this survey. Our survey results, although parent-reported and retrospective in nature, confirm previous reports that consideration could be made for using alternative diets in the GLUT1DS population, especially in the long-term, to improve side effects and tolerability when deemed medically appropriate [10–13]. In our clinical experience at our institutions, we have both started and transitioned GLUT1DS patients to these alternative diets during adolescence with preliminarily good results. In a few patients who have had worsening of seizures, restarting a high ratio KD has led to rapid resumption of prior seizure control.

This survey highlights multiple areas of future research. The majority of families reported checking serum ketones and often noted a correlation between ketone levels and seizure control. However, those who checked serum ketone levels were no more likely to achieve seizure freedom than those how did not. A prospective trial comparing blood with urine monitoring might be of importance, especially as daily fingersticks for a child with a disability can be burdensome and expensive to a family. This survey also indicated that puberty may be a time of concern for patients with GLUT1DS on diets. There are indications that this may be a time of change for all dietary therapy patients regardless of etiology as well as for epilepsy patients in general [28]. Dietary therapies appeared overall similar; therefore a prospective trial of either lower ratio KD or the MAD for newly-diagnosed GLUT1DS (with an ability to switch to a more restrictive KD allowed) may be justified. In addition, a prospective trial including EEG would avoid any placebo effect or over-estimation of the true benefit of dietary therapy (or any version of this treatment). Finally, patients were receiving a wide variety of dietary supplements. These supplements were likely intended to boost ketosis as well as to improve tolerability and reduce side effects. Although carnitine was used by half, and has been suggested by some centers for empiric use, these results showed no preferential outcomes [2,24]. Trials of these supplements in children with GLUT1DS on dietary therapy therefore, especially MAD and LGIT, are warranted. Lastly, even though this is the largest cohort of GLUT1DS patients reported with dietary therapy, future prospective studies with larger numbers may allow for more definitive statements to be made about statistical correlations and benefits of individual diets.

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Author contributions

- Ms. Kass carried out the initial analyses, drafted the initial manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted.
- Dr. Winesett helped with conceptualization of the study, survey questions to ask, reviewed and revised the manuscript, and approved the final manuscript as submitted.
- Ms. Turner provided guidance regarding nutrition questions, reviewed and revised the manuscript, and approved the final manuscript as submitted.
- Ms. Bessone provided guidance regarding nutrition questions, helped coordinate survey collection, reviewed and revised the manuscript, and approved the final manuscript as submitted.
- Dr. Kossoff conceptualized and designed the study, distributed the survey, collected surveys, supervised data collection, helped with analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Conflict of interest

Dr. Kossoff is on the Scientific Advisory Board for Atkins Nutritionals, Inc.

Ms. Turner and Ms. Bessone are Consultants for Nutricia, Inc.

Hannah Kass and Dr. Winesett have no conflicts of interest relevant to this article to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2016.01.011.

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