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How often is antiseizure drug-free ketogenic diet therapy achieved?

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ABSTRACT

The ketogenic diet (KD) is often started not only for seizure reduction but also to potentially wean antiseizure drugs (ASDs) in children with epilepsy. Although there have been several publications regarding ASD reduction on the KD, it is unknown how often complete medication withdrawal occurs. We reviewed the charts of all children started on the KD at Johns Hopkins Hospital and Johns Hopkins All Children's Hospital from 1/11 to 4/18. Children were defined as achieving drug-free diet (DFD) status if they started the KD on at least 1 ASD and achieved a period of time where they were on the KD alone. Over the time period, 232 children were evaluated; DFD status occurred in 43 (18.5%), of which 32 (13.8% of the full cohort) remained off ASDs for the remainder of their KD treatment course. Eleven children restarted ASD after a mean of 7 months. Children achieving DFD therapy were more likely to be younger, have fewer ASDs at KD onset, have Glut1 deficiency or epilepsy with myoclonic–atonic seizures, but were less likely to have Lennox–Gastaut syndrome or a gastrostomy tube.

1. Introduction

The ketogenic diet (KD) is a high-fat, low-carbohydrate, and adequate-protein therapy that has been used increasingly for refractory epilepsy [1]. Most pediatric patients have attempted unsuccessfully at least two antiseizure drugs (ASDs) prior to starting the KD and remain on at least one drug at onset [2,3]. One of the major goals of parents when starting the KD is to reduce and even discontinue ASDs [4,5]. This is typically done at 1 month on the KD, slowly, and one ASD at a time [2,6].

Although we often tell families that the KD and ASDs are a "partnership" and that most children will need to remain on an ASD while on the KD, the true incidence of being able to discontinue all ASDs is not known. One study reported 10 adults who were drug-free with the modified Atkins diet, but this was at diet onset rather than describing actual ASD discontinuation [7]. More information on achieving complete medication freedom is needed to better set expectations and improve anticipatory guidance.

The purpose of this study was to investigate the following: 1) how often children on ASDs at KD onset achieved complete medication freedom, 2) how long durations of medication freedom lasted, 3) which seizure etiologies were more likely to be able to be drug-free on the KD, and 4) when and why some children restarted ASDs.

2. Methods

2.1. Patients included

All pediatric patients admitted for initiation of the classic KD at both the Johns Hopkins Hospital and Johns Hopkins All Children's Hospital from January 2011 to April 2018 were consented and prospectively enrolled in our database. Children were excluded if they were started on the KD without any ASD (n = 9), as they, therefore, had no drugs to potentially wean, and these children have been previously described in the literature [8,9]. Information was obtained by chart review, including emails, clinic visits, and phone calls. Medication withdrawal was often suggested and planned in clinic visits with updates done by phone or email. Seizure reduction was documented by parental report and calendars at clinic visits, email correspondence, and phone conversations. Typically, our centers would wait at least one month before starting to wean ASDs to allow for assessment of KD response. Children that were lost to follow-up were documented as having stopped KD at last contact. Drug-free diet (DFD) status was defined as such if a child started the KD on one or more ASD and achieved at least one week where they were on solely on the KD without any ASDs. Duration of DFD status was documented as well as if any ASD was restarted.

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2.2. Statistics and consent

p value of less than 0.05 was considered to be statistically significant. Chi square, t test, and Fisher Exact tests were performed to assess differences between study groups. All parents were consented to have their child's information in a prospective database approved by the Johns Hopkins Hospital Institutional Review Board.

3. Results

3.1. Study population

From January 2011 to April 2018, 241 consecutive pediatric patients were initiated on the KD at our two centers, of which 232 children were on ASDs. Overall demographics were similar to most KD-published populations and are listed in Table 1. The population mean age was 4.7 years (range: 0.3–21 years), with 49.1% female, and 78.9% with at least mild intellectual disability. Children had a mean of 21.7 seizures per day (range: 0.05–240 seizures). The most common seizure types were infantile spasms and Lennox–Gastaut syndrome (both 20.7%), with the next most common types being epilepsy with myoclonic–atonic seizures (Doose syndrome) (7.8%), Dravet syndrome (6.0%), Glut1 deficiency (3.0%), Rett syndrome (1.7%), and pyruvate dehydrogenase deficiency (PDH) (1.3%). In regard to KD provision, 47% of children were receiving solid KD foods, 35% were on formula only, and 18% were on a combination; 38% were fed via gastrostomy tube. Overall outcomes were also excellent and similar to published reports. After three months on the KD, 70% had greater than 50% seizure reduction, 20% were seizure-free. At the time of analysis, 21% of patients were still on the KD. This study analysis was completed in August 2018.

3.2. Drug withdrawal and discontinuation

At KD onset, children were on a mean of 2.4 ASDs (range: 1–6), with the most common including levetiracetam (n = 132), valproate (n = 71), clobazam (n = 57), lamotrigine (n = 35), and rufinamide (n = 24). Forty-three patients (18.5%) achieved DFD status, 32 (74%) of whom remained off all ASDs for the remainder of their KD treatment course; hence, 32/232 (13.8%) achieved lasting ASD freedom. The most common final ASD weaned was levetiracetam (28% of patients), followed by valproate (16%), and clobazam (12%).

The reasons for attempting to wean all ASDs were 1) seizure freedom and 2) excellent (50–99%) seizure control through KD. For those who achieved DFD status, 63% were seizure-free, 28% had a 90–99% seizure reduction, and 9% had a 50–90% seizure reduction. No child in this cohort was able to stop all ASDs with a concurrent <50% seizure reduction due to the KD. Drug-free diet status was achieved after a mean of 7.5 months on the KD (range: 1.5–21 months), and the KD then was maintained (without ASDs) for a mean duration of 22.6 months (range: 1–66 months).

Table 1
Patient demographics (n = 232).

Age (years) at KD start, mean (range)	4.7 (0.3–21)
Number of ASD at KD onset, mean (range)	2.4 (1–6)
Female, n (%)	114 (49%)
Intellectual disability, n (%)	183 (79%)
KD provision, n (%)	
Solid foods	109 (47%)
Formula/liquid foods	81 (35%)
Combination of the above	42 (18%)
Gastrostomy tube, n (%)	88 (38%)
Seizure etiology or syndrome, most common, n (%)	
Infantile spasms	48 (21%)
Lennox–Gastaut syndrome	48 (21%)
Epilepsy with myoclonic-astatic seizures	18 (8%)
Dravet syndrome	14 (6%)
Glut1 deficiency syndrome	7 (3%)
Rett syndrome	4 (2%)
Pyruvate dehydrogenase deficiency	3 (1%)
Seizures per day, mean (range)	22 (0.05–240)
KD duration (months), mean (range)	20 (0.1–80)

3.3. Characteristics of children who had to restart ASDs

The majority of children had no increase in seizure frequency upon weaning the last drug. Eleven children restarted ASDs after a mean of 7 months (range: 1–50 months), typically for increased seizures but at times due to stable, but continuing seizures. These 11 children subsequently remained on the KD for a mean of 11.7 additional months. Two children were weaned off of all ASDs a second time after prior, temporary DFD therapy status; one child successfully remained on DFD therapy afterwards whereas the other child eventually was started on oxcarbazepine.

3.4. Children achieving complete ASD freedom

Factors influencing likelihood of DFD status are listed in Table 2. Children achieving DFD therapy were more likely to be younger (3.8 vs. 4.9 years, $p = 0.02$), on fewer ASDs at KD onset (1.7 vs. 2.6, $p < 0.001$), have Glut1 deficiency (12% vs. 1%, $p = 0.003$) or epilepsy with myoclonic–atonic seizures (Doose syndrome) (26% vs. 4%, $p < 0.001$), but were less likely to have Lennox–Gastaut syndrome (5% vs. 24%, $p = 0.004$) or have a gastrostomy tube (21% vs. 42%, $p = 0.009$). Two of the three children with pyruvate dehydrogenase deficiency became drug-free as well. No particular final ASD was associated with greater ability to achieve DFD status.

4. Discussion

Achieving complete ASD freedom while on the KD occurred in approximately 1 in 5 children in our series, and for a lasting duration (at least until KD discontinuation in this cohort) for 1 in 7. For families contemplating the KD as a therapeutic option, or for those already on the KD, we hope this will help guide conversations on expectations. It is important to realize that 4 out of 5 patients needed to remain on drugs, suggesting that the concept of an ASD–KD partnership is true for most children. In addition, 1 out of 4 children who did stop all ASDs had to restart one, sometimes after only a few months, and several stopped the KD shortly afterwards. Levetiracetam was the most common last ASD weaned, possibly due to its frequent use and favorable side-effect profile, particularly recognizing the potential risks of the KD combined with topiramate, zonisamide, and valproate [2,10].

Younger children on fewer medications, with excellent seizure reduction, and especially those with Glut1 deficiency and Doose syndrome, were most likely to become drug-free. Conversely, children with Lennox–Gastaut syndrome and those with gastrostomy tubes

Table 2
Patient characteristics associated with likelihood of successfully stopping all antiseizure drugs on the ketogenic diet.

	Achieved DFD therapy (n = 43)	Still on ASD (n = 189)	p value
Age (years) at start, mean	3.8	4.9	0.02
Number of ASD at KD onset (mean)	1.7	2.6	<0.001
Female (%)	47%	50%	0.70
Vagus nerve stimulator present (%)	2%	7%	0.23
Gastrostomy tube (%)	21%	42%	0.009
Glut1 deficiency (%)	12%	1%	0.003
Doose syndrome (%)	26%	4%	<0.001
Lennox–Gastaut syndrome (%)	5%	24%	0.004
Last ASD weaned was valproate (%)	26%	31%	0.47
Last ASD weaned was levetiracetam (%)	47%	58%	0.16

were less likely to achieve complete medication freedom. While the majority of these predictive factors are intuitive, it is less clear why those with gastrostomy tubes remained on ASDs. One explanation may be that providing ASDs via gastrostomy tube is easy; there would be fewer difficulties with children refusing medication tastes and thus less impetus to stop. Reduction of ASDs to improve quality of life can be attempted in all children on the KD with seizure improvement; even if unsuccessful, it may be worth the attempt. As recommended in 2018 by the International Ketogenic Diet Study Group, a child does not need to be seizure-free in order to attempt ASD discontinuation [2]. However, should the ASD have benefits for comorbidities (e.g., mood or migraine), achieving drug-free KD status may have negative consequences and may not be warranted.

There are several limitations of this study. We did not routinely check EEGs at KD follow-up, which could have supported (or prevented) the decision to stop the final ASD and been evaluated as a predictive factor for success. In addition, this was only a dual-center study; other centers may have different protocols for reducing and thresholds for restarting ASDs. Another limitation is that several children were lost to follow-up and may still be on the KD with ASD freedom, suggesting an even longer DFD period than the mean of 23 months. Finally, most decisions regarding when to start or stop interventions are subjective and frequently parent-influenced; prospective, protocolized studies may be valuable.

5. Conclusion

In summary, sustained freedom from all ASDs can be possible for a sizeable percentage of children with refractory epilepsy who achieve seizure control with the KD, often for extended periods of time. Predictive factors do exist as well, all of which can be helpful when counseling families about the likelihood of discontinuing all drugs should the KD be started.

Ethical statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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