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Short communication

High-fat diets and seizure control in myoclonic-astatic epilepsy: A single center's experience

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ABSTRACT

Purpose: To determine the efficacy of the Modified Atkins Diet (MAD) and Ketogenic Diet (KD) in seizure control within a population of myoclonic-astatic epilepsy (MAE) patients.
Methods: This was a retrospective, single center study evaluating the seizure control by high fat diets. Seizure diaries kept by the parents performed seizure counts. All patients met the clinical criteria for MAE.
Results: Nine patients met the clinical criteria. We found that both the MAD and KD were efficacious in complete seizure control and allowed other medications to be stopped in seven patients. Two patients had greater than 90% seizure control without medications, one on the KD and the other on the MAD. Seizure freedom has ranged from 13 to 36 months, and during this time four patients have been fully weaned off of diet management. One patient was found to have a mutation in *SLC2A1*.
Conclusion: Our results suggest that strictly defined MAE patients respond to the MAD with prolonged seizure control. Some patients may require the KD for seizure freedom, suggesting a common pathway of increased requirement for fats. Once controlled, those fully responsive to the Diet(s) could be weaned off traditional seizure medications and in many, subsequently off the MAD or KD.

1. Introduction

Doose syndrome is a primary generalized idiopathic seizure disorder. Since the 1970s, the phenotype and nosology have continued to evolve. Doose syndrome was originally noted to be a generalized cryptogenic or sympathetic seizure disorder. However, largely based on Doose's original description, in 1989 and then in 2010, the International League Against Epilepsy (ILAE) defined Doose syndrome as myoclonic-astatic epilepsy (MAE) with (1) normal development before the onset of seizures; (2) onset of myoclonic, myoclonic-atonic, or atonic seizures between 7 months and 6 years of age; (3) the presence of generalized spike or polyspike wave EEG discharges; and (4) renamed MAE as myoclonic-atonic seizures.[1,2] Initial EEGs are usually normal but with time show bursts of irregular generalized 2–5 Hz spike/polyspike and wave complexes. For continuity, we will use the term MAE for the article.

Historically, medical treatment of seizures in MAE has been unsatisfactory, with seizure freedom only ranging from 0 to 36%.[3,4] Recently, the Ketogenic Diet (KD) has been shown to have superior efficacy compared to traditional medical treatments.[3–6] Limited data suggests the Modified Atkins Diet (MAD) has efficacy, but the total number with MAE are limited and only two studies specific to this condition using the MAD exists to our knowledge.[7,8] However, there is little data on long-term outcome using either diet. Here, we describe our center's data on MAD/KD in patients with MAE.

2. Methods

The Institutional Review Board at Seattle Children's Hospital approved this retrospective study. Nine patients met the criteria for MAE and were on the MAD or KD (Table 1). All patients were followed for at least 9 months following initiation of MAD or KD.

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Table 1
Patient demographics seizures and EEG findings.

Patient	Sex	Age of first seizure (months)	Seizure types	Febrile seizures onset (months)	EEG
1	Male	26	A/GTC/M	No	GS-GPS/F
2	Male	22	A/GTC/M	No	GS
3	Male	35	A/GTC/M/AA/T	No	GS
4	Male	27	A/GTC	No	GS
5	Male	24	A/GTC/M/AA	Yes (12)	GS
6	Male	19	A/GTC/M	Yes (18)	GS
7	Male	29	A/GTC/AA/M	No	GS
8	Female	22	A/AA	No	GS
9	Male	40	A/GTC/AA/M	No	GS-GPS

Seizures: A, atonic seizure; GTC, Generalized tonic/clonic seizure; M, myoclonic seizure; AA, atypical absence seizure; T, tonic seizure. EEG: GS, generalized epileptiform discharges; GPS, generalized polyspikes; F, focal discharges.

Seizure frequency was documented by seizure diaries compiled by the families and were reviewed at each clinic visit (Table 2).

Due to perceived compliance issues, several families elected to start the MAD. Briefly, the traditional KD (4:1 ratio) has only 2% carbohydrate, 8% protein and 90% fat. The MAD (20 g of carbohydrate per day) has 6% carbohydrate, 30% protein, and 64% fat. The MAD is less restrictive in food choices and hence more adaptable to patient food tastes. The MAD used in our study contained 10–20 g/day of carbohydrate.

All patients underwent magnetic resonance imaging (MRI). Multiple EEG studies ($n = 2$–8) were performed in all patients at our Institute and reviewed by one of the authors (RPS).

Genetic testing was performed using massive parallel sequencing of known epilepsy genes (Courtagen Life Sciences, Woborn, MA). In 4/9 patients, genetic testing was not performed due to insurance reasons or family preference.

3. Results

Nine patients were identified with the median age at onset at 2 years (Table 1). All patients had atonic seizures as well as other seizure types (Table 1). Atonic seizures were clinically described as head drops or brief loss of tone. Video-EEG studies were not performed on all patients and seizure semiology was inferred by parental description. All patients reported multiple daily or monthly seizures prior to initiation of MAD or KD. By parental report, all but Patient 3 had normal early development. Patient 3 had mild delay in expressive language, not gaining two-word sentences until 2 years of age and more complex sentences until 3 years of age after which seizures began. MRI scans of the brain were all considered to be normal. EEG studies demonstrated generalized spike and wave discharges in all patients with a single patient also having infrequent focal discharges (Table 1).

Patient 8 was found to have a known pathological missense mutation, c.376C > T (p.ARG126Cys) in the Helix 4 portion of *SCL2A1*.

The age of diet initiation ranged from 19 to 61 months of age. Seven of the nine patients became seizure free within several weeks of dietary therapy, suggesting a very quick and complete response to dietary management. In addition to the rapid response, the MAD or KD induced a seizure freedom between 2 and 4 years (Table 2).

Unfortunately, Patient 7 could not tolerate the long-term use of the KD. The KD was stopped after several years due to compliance and the patient had to be restarted on medications with ongoing infrequent seizures. Patient 6 continued to have seizures on the KD and parents stopped the diet and returned to medications. He is currently having similar seizure frequency as compared to prior to the KD.

Seven patients achieved continued seizure freedom on the MAD or KD in the context of stopping all traditional seizure medications. Patients 3 and 4 have been successfully weaned off the MAD and have remained seizure free for 6–22 months. Patients 1 and 2 have also been successfully weaned off the KD. Patient 2 required increasing the fat ratio from the MAD to the KD to become seizure free. He could still be successfully weaned off the diet and remain seizure free. In Patients 1–4 a total of up to 36 months of seizure freedom off the MAD or KD and all other seizure medications. In those four patients still on the MAD, a total of 13–36 months of seizure freedom have been obtained.

4. Discussion

MAE is a distinct electro-clinical syndrome.[3] Treatment can be problematic but some studies indicate that the KD can significantly reduce seizures; with up to 39% (33/85) becoming seizure free.[4,8,9]

Table 2
Seizure medication use before diet initiation and diet characteristics for seizure control.

Patient	Seizure medications	Diet	Seizure types and frequency (per day)	
		Keto Diet ratio/MAD (months to diet onset)	Before diet	After diet
1	LEV, LTG, VPA, RUF	KD 4:1 (8)[#]	2-GTC; 20-A; >25-M	0
2	LEV	MAD (2) > 4:1 (3)[#]	3-GTC; 40-A	0
3	LEV, VPA, LTG, RUF, ZNS, CBZ	MAD (4)[#]	2-GTC; >15-A; >20-M	0
4	LEV, TPM	MAD (6)[#]	5-D; 3-GTC (lifetime)	0
5	LEV, LTG, PB, OXC, VPA, RUF, TPM	MAD (38)	>10-A; 4-D; 1-M*	1-M*
6	LEV, VPA, TPM	KD 4:1 (12)	15-D: >25-M: <1-GTC	3-GTC*
7	LEV, LTG, VPA,	KD 4:1 (6)	7-D: 10-M: 50-A	0^
8	LEV, LTG, VPA, ZNS	MAD (8)	>8 A*: 5-D (lifetime)	0
9	LEV, LTG, VPA, ZNS	MAD (45)	35-M: 20-D: 3-GTC (lifetime)	0

Abbreviations: Seizure Medications: LEV, levetiracetam; LTG, lamotrigine; TPM, topiramate; VPA, valproic acid; RUF, rufinamide; ZNS, zonisamide; CBZ, carbamazepine; OXC, oxcarbazepine. Diet: KD, ketogenic diet; MAD, Modified Atkins Diet; Patient 2 was started on the Modified Atkins Diet but continued to have seizures and was switched to the ketogenic diet. [#]Currently weaned off diet and off medications and no seizures reported. Seizure types: GTC, generalized tonic clonic; A, atypical absence; D, drop; M, myoclonic. Seizure frequency: * represents seizures per month; ( ) represents limited seizure frequency; Patient 5 having one myoclonic seizure per month; Patient 5 currently having three GTC per month on ketogenic diet; ^Patient 7 patient was seizure free on the ketogenic diet but did not tolerate diet and was placed on VPA and LTG and was seizure free but has since been lost to follow-up.

The response to the KD has been significant enough that the International Ketogenic Diet Working Group identified MAE as one of the epilepsy syndromes responsive to the KD.[10] The use of the MAD is less well documented. In a small group of patients, the MAD decreased seizure frequency, but no patient became completely seizure free.[7–9,11]

Our population of nine patients had a significant response to seizure reduction using the MAD or traditional KD (Table 2). All but two patients became seizure free on the KD or MAD. Five patients started on the MAD and one patient on the KD became completely seizure free. At 12–15 months of seizure freedom, medications were weaned off one-at-a time over an 8–10 week period. No patient had break through seizures during the weaning period of any of the medications.

EEGs were repeated in seven of the nine patients during seizure freedom while on one of the Diets. Of those, five continued to show interictal generalized epileptiform discharges and two had normal studies. One of the patients with a normal EEG stopped the diet and seizures returned (Patient 7) together with abnormal EEG findings similar to before starting the KD. Response to treatment was however, determined based on the clinical picture and not EEG findings.

One patient initially started on the MAD with modest efficacy (>70% seizure reduction, data not shown), only became seizure free when transitioned to the KD. This suggests that a "dose–response" of increased fat ratio was required for seizure freedom, as supported by the raised overnight fasting beta hydroxybutyrate from an average of 4.5–5.5 mM on the MAD to 7.1–7.9 mM on the KD. However, we do not know the exact beta hydroxybutyrate level at the time of seizure events while on the MAD, nor can we rule out that a more stable state of ketosis on the KD and not the absolute ketosis was the etiology of better seizure control. Taken together our data suggest that the Diets (KD/MAD) induce long-term seizure freedom that is not dependent on traditional medications. Overall, over 78% (7/9) became seizure free on one of the diets. Dietary control of seizures also extended to the removal of all traditional seizure medications, suggesting a pathway(s) of seizure control elicited by the KD/MAD alone.

Two patients (Patients 6 and 7) raised several important points about using the MAD and/or KD to control seizures. Patient 7 became seizure free on the KD, but was unable to tolerate the long-term use of the diet. When switched to traditional seizure medications, this patient began having break through seizures and, unfortunately, was lost to follow-up. Would the less restrictive and more tolerable MAD have been an option for seizure control in this patient? Another question is the incomplete control of seizures in some patients. Patients 1–5 and 9 became seizure free on the KD/MAD without seizure medications. By contrast, Patient 6 did not become seizure free and also had difficulty tolerating the KD. As the diet has been weaned off, his seizure frequency has returned to pre-KD numbers (data not shown). Within our MAE population, there were MAD/KD non-responders as well as patients in whom the benefits of the diet did not remain after diet discontinuation. Our data further validates distinct categories of MAE etiology exist.[8,12]

Patient 8 had Glut 1 DS due to mutations in the *SLC21A* gene. This patient did not have the usual findings associated with the classical Glut 1 DS or reported extended phenotype recently described with this syndrome, including the early-onset absence seizures.[13] This suggests that a population of patients with generalized seizures can be identified with Glut 1 DS based on complete control of seizures on dietary treatment, without exhibiting the full features of Glut 1 DS.

Unfortunately, our data does not provide clues regarding which MAE patients should be started on the MAD or KD. All patients were proved to be early medically intractable due to failure of >2 medications within 2 years of seizure onset, with the exception of Patient 2.[14] Neither the number of medications tried, nor the seizure frequency or semiology was informative concerning diet selection. Our data has a strong selection bias due to its retrospective nature and due to the use of only patients who met the clinical criteria of MAE and were placed on the KD or MAD. The literature is clear that at other centers the MAD and KD were not 100% successful.[4,7–9,11] However, even given inherit problems in our retrospective study, we think one strategy might be to initiate the MAD and then transition those patients who do not adequately respond to the KD.

Conflict of interest

None.

Disclosures

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