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Review Article

Ketogenic diet: a promising alternative nonpharmacology treatment for pediatric epilepsy

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ABSTRACT

Epilepsy is a syndrome of brain dysfunction induced by the aberrant excitability of certain neurons. Despite advances in surgical technique and anti-epileptic drug in recent years, recurrent epileptic seizures remain intractable and lead to a serious morbidity in the world. The ketogenic diet (KD) is a nonpharmacologic treatment that has been used for refractory epilepsy since 1921. The KD is a high-fat, low-carbohydrate, and restricted protein diet, which is calculated and weighed for each individual patient. The goal of the KD treatment is to bring the brain into a state of ketosis to control seizures. Many studies have shown that ketogenic diet was very useful in controlling refractory epilepsy.

Keywords: Ketogenic diet, Nonpharmacology, Pediatric epilepsy, Pediatric, Seizure

INTRODUCTION

Epilepsy is the most common serious neurological condition in the world, with an estimated prevalence of 1% of the population. The highest incidence occurs in childhood and in the elderly, and with lower levels in early adulthood.[1] According to WHO in 2017, there were approximately 2.4 billion people diagnose with epilepsy ever year around the world. The lifetime risk of developing epilepsy is 3.9%, with males have slightly higher risk than women.[2]

REVIEW OF LITERATURE

Traditional epilepsy management includes pharmacological treatment and surgery. Despite these therapies, 25% of children continue to have uncontrolled seizures. Deliberate fasting has been shown to control seizures. The impracticality of prolonged starvation became the drive to formulate the ketogenic diet. KD is a treatment option for many of these children. A meta-analysis of 19 studies with a combined sample of 1084 pediatric patients was complete in 1998 by Blue Cross Blue Sheld. Estimates of the overall efficacy of the KD in controlling seizures were reported as follows 16% became seizure free, 32% had a >90% reduction in seizures and 56% had a >50% reduction. KD is high in fat, moderate in protein, and low in carbohydrates.[1] Now days the ketogenic diet was rarely used as the adjuvant therapy for epilepsy in children despite numerous evidence the efficacy of it.

DEFINITION

Seizure is defined as an excessive burst of abnormal synchronized neuron activity affecting small or large neuronal networks that results in clinical manifestations that are sudden, transient and usually brief.

Epilepsy is a disorder of the brain characterized by any of the following conditions:

- At least two unprovoked seizures occurring >24 hour apart
- One unprovoked seizure and a probability of further seizures similar to the general recurrence risk after two unprovoked seizures, occurring over the next 10 years
- Diagnosis of an epilepsy.[3]

ETIOLOGY

A seizure may be an isolated event with no obvious cause or triggered by acute metabolic disturbances or fever. Epilepsy may be idiopathic (usually genetic), cryptogenic (undiagnosed cause with associated neurological or developmental deficits), or symptomatic (known cause).

CLASSIFICATION

Seizures can be clinical or subclinical (electrographic) with EEG but no clinical manifestations. The International league against Epilepsy (ILAE) classification system is summarized in Figure 1.[4]

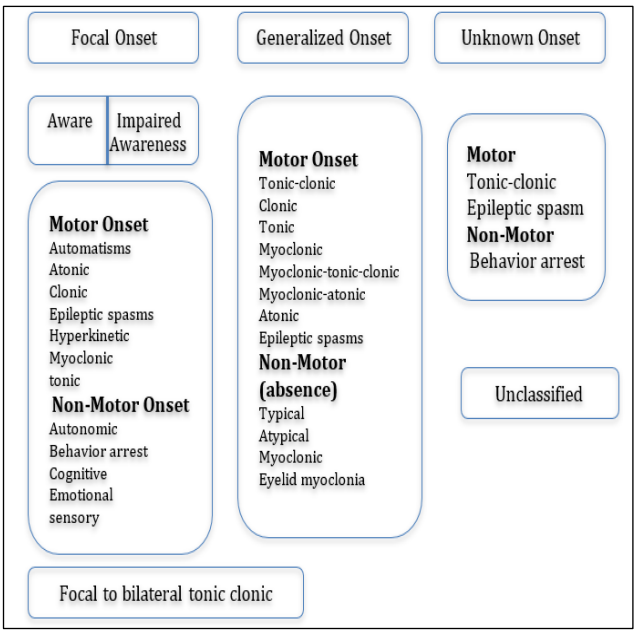

Figure 1: ILAE 2017 classification of seizure types.[4]

MODE OF SEIZURE ONSET

Generalized epileptic seizure are those that originating at some point within and rapidly engaging, bilaterally distributed networks, which can be subcortical or cortical structures, but do not essentially, include the entire cortex.

The term focal can be replaced with partial epileptic seizures, which are origination within one hemisphere. They may be localized or widely distributed. Focal seizures may originate in subcortical structures.[3]

TYPES OF SEIZURES

The type of seizures is summarized on Table 1.

PATHOPHYSIOLOGY

One commonality across epilepsies is a disrupted imbalance between excitatory (via glutamatergic signaling) and inhibitory (via GABAergic signaling) drive at the synaptic level that can result in seizure activity.[5] A seizure results when a sudden imbalance occurs between the excitatory and inhibitory forces within the network of cortical neurons. The basic physiology of a seizure episode is detected to in an unstable cell membrane or its surrounding supportive cells. The seizure originates from the grey matter of any cortical or subcortical area. Initially a small number of neurons fire abnormally. Normal membrane conductance and inhibitory synaptic current breakdown and excess excitability spread either locally to produce a focal seizure or more widely to produce a generalized seizure. This onset propagates by physiologic pathways to involve adjacent to remote areas. As abnormality of potassium conductance, a defect in the voltage activated ion channels, or a deficiency in the membrane ATPase linked to ion transport may cause neuronal membrane unstable and cause a seizure. Certain neurotransmitters (e.g. glutamate, aspartate, acetyl choline, norepinephrine, histamine, corticotrophin releasing factor, purines, peptides, cytokines and steroid hormones) enhance the excitability and propagation of neuronal activity, whereas a-amino butyric acid (GABA) and dopamine inhibit neuronal activity and propagation.[6]

DIAGNOSIS

Diagnosis in epilepsy include establishing a seizure diagnosis and an etiologic diagnosis and identification of precipitating factors. This is accomplished by combination of history taking, physical examination, electroencephalographhy (EEG) and laboratory examinations.[7] Diagnosis algorithm can be seen in Figure 2.

MANAGEMENT Of EPILEPSY

Pharmacology

Long term AED treatment should be started after the second seizure. The aim of the treatment is complete seizure control without significant adverse effects. All drugs are started in low dose and increased gradually up to a maximum dose till seizure control is achieved or side effects appear. If no control is obtained with maximum dose of first drug, then a second first line drug is initiated, and the first drug tapered. If partial contol is achieved, then a second AED should be added. Four major first line conventional anticonvulsants were phenobarbitone, phenytoin, valproate, and carbamazepine. Carbamazepine and valproate appear to be better tolarated than

phenobarbitone and phenytoin. AED is withdrawn after 2 year of seizure freedom. All the drug dosage and usage can be seen in Table 2.[7] And the algorithm of status epilepticus management can be seen in Figure 3.

REFRACTORY EPILEPSY

Refractory epilepsy can be defined as epilepsy which is uncontrolled despite adequate trials of three first line AEDs and when it disrupts developmental progress or normal childhood activity. When faced with a child with uncontrolled epilepsy, always try and confirm whether the diagnosis is correct. Often non-epileptic conditions may be confused as seizures. The type of seizure and a correct diagnosis of the specific epilepsy syndrome may facilitate correct DOC. It is best to refer refractory epilepsy early to a tertiary center for appropriate evaluation (including highend MRI, video EEG etc.) and to get guidance on management options like newer AEDs, ketogenic diet and surgery.[7]

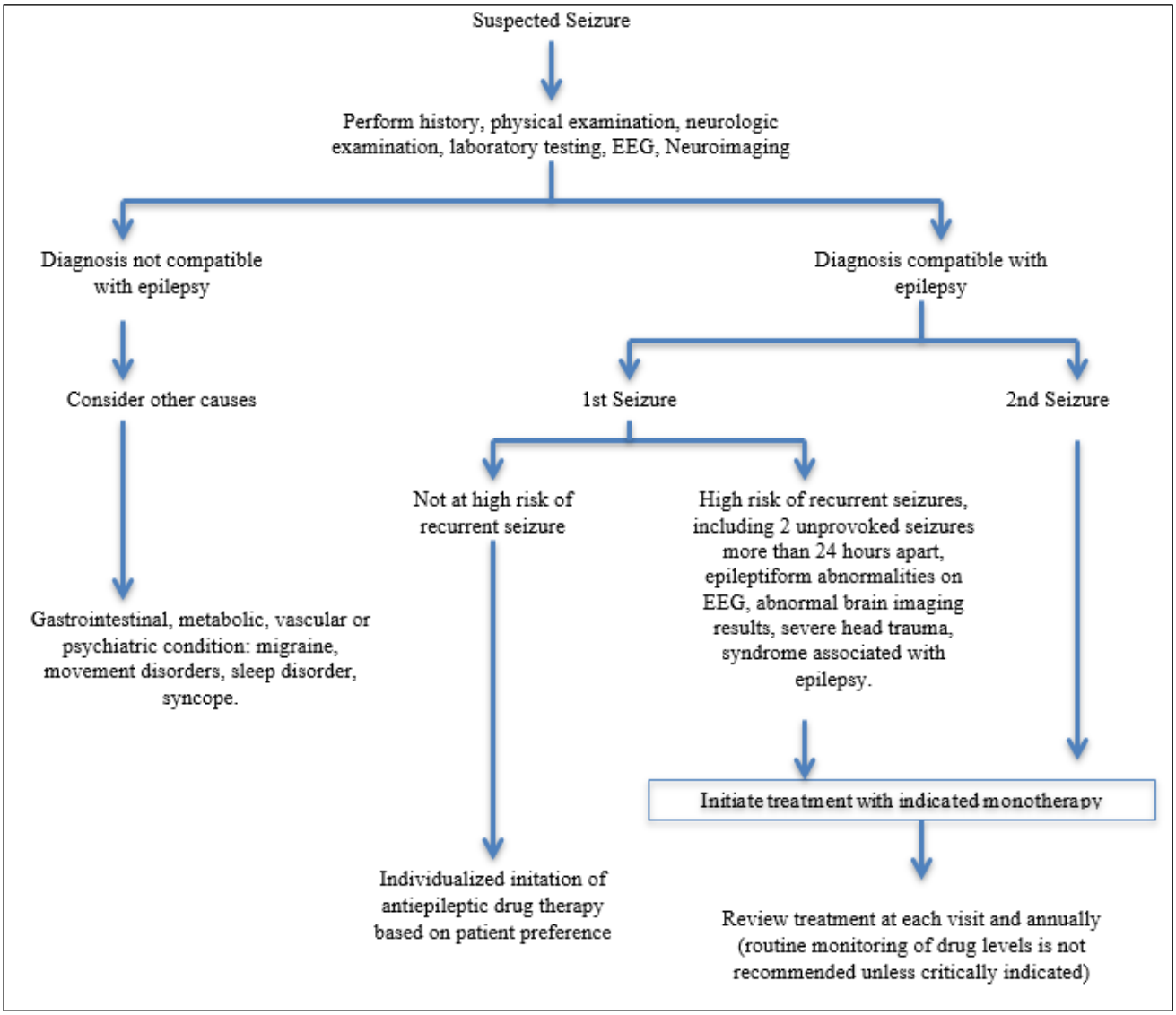

Figure 2: Diagnostic algorithm for epilepsi.[2]

SURGERY INTERVENTIONS

Up to 30% of patients with epilepsy can have medically refractory epilepsy. Surgical resection of the seizure focus in appropriately selected patients often results in decreased frequency or elimination of seizures with improvement in quality of life. Seizure freedom is achieved in up to 76% of patients after resection.[2] Patients with intractable epilepsy resulting from metabolic or degenerative problems are not candidates for respective epilepsy surgery. Focal resection of the epileptogenic zone is the most common procedure.[3]

Table 1: Types of seizures.[3,4]

Types of seizure	Characteristics	Consciousness	EEG
Absence seizure (Petit mal)	• Generelized seizures • A sudden onset behavioral arrest, blank stare, unresponsiveness and sometimes a brief upward rotation of the eyes. • Duration: few seconds to 1/2 min	Little tonopostictal confusion, the patient resumes the activity he/she was doing prior to the seizures	Pathognomonic: bilaterally synchronous and symmetric paroxysms of spike-and-wave complexes at a frequency of 3 hz appear during seizure
Myoclonic seizure	• A sudden, brief, irregular and shock like contractions that may be generalized or confined to the face and trunk, or to one or mor extremities, or even to individual muscles. Can evolve into tonic clonic • A single or repetitive twitch to a sever jerking, symmetric/ asymmetric	• No postictal confusion • No impaired consciousness	Brief generalized polyspikes or polyspikes and wave discharges with the myclonic jerk
Clonic seizures	• Repetitive rhythmic clonic jerks • A short postictal phase • Can lead to tonic clonic seizure	Impairment of consciousness	Generalized polyspikes and wave discharges or generelized fast activity
Tonic seizures	• Brief seizures consisting of sudden onset of increased tone in extensor muscles • Longer than myoclonic seizures	Altered consciousness	Slowing of the background with multifocal spikes, sharp waves and bursts of irregular spike and wave activity
Tonic clonic (Grand Mal)	• Tonic extension and then clonic convulsive movements of all extremities. • May associated with aura (suggesting a focal origin of epileptic discharge)	Altered consciousness	• Generalized repetitive spikes in the tonic phase and then periodic spikes in the clonic phase. • In between attacks, may discharged brief generalized spikes or spike wave that are polymorphic
Epilepsy syndromes	A unique epilepsy condition with different etiologies that involve more than just a seizure type		
Status epilepticus	A seizure or series of seizures, which continue for at least 30 minutes	Without return of consciousness between the seizures	

KETOGENIC DIET

Nonpharmacologic approaches may be useful adjuncts in patients with difficult-to-control seizures or who find medication difficult to tolerate. One of the nonpharmacology therapy for those patients are ketogenic diet (KD). KD is a stringently controlled high fat and low protein/carbohydrate diet given with/without a restricted fluid intake to maintain ketosis on a long-term basis. It has been shown that it is more efficacious than newer AEDs in controlling refractory seizures and is more cost effective.[7] The diet was designed to stimulate the ketosis of starvation by supplying fat as the main source of calories, while restricting protein and carbohydrate consumption. The exact mechanisms of seizure inhibition remain unknown, but its neuroprotective effects were demonstrated in the animal research, which no other antiepileptic therapy has provide.[1] The "classic" KD is based upon consumption of long-chain saturated triglycerides in a 3:1-4:1 ketogenic diet ratio of fats to carbohydrates+protein (by weight). The vast majority of calories (>90%) are derived from fat. Diet treatment generally begins with a period of fasting followed by gradual increase in calories to a target KD ratio of 3:1-4:1. This is conducted in the inpatient setting over the course of several days, where blood glucose, urine ketones, and several other metabolic variables are closely monitored. The hallmark feature of KD treatment is the production of ketone bodies by the liver. Ketone bodies provide an alternative substrate to glucose for energy utilization, and in developing brain, also constitute essential building blocks for biosynthesis of cell membranes and lipids.[8] Initiation of KD most often occurs in an inpatient setting at an epilepsy center in order monitor the patients. Traditionally, the diet is initiated after a 24-48 hour fasting period, and it is slowly introduced until the patient successfully achieves the full ketogenic diet to be discharged home with. The average

hospital stay is four days, during which the family and the patient are educated on the diet. If ketosis is not maintained, the patient must return to the hospital to restart the entire diet initiation process, therefore, compliance with the diet is essential.[9]

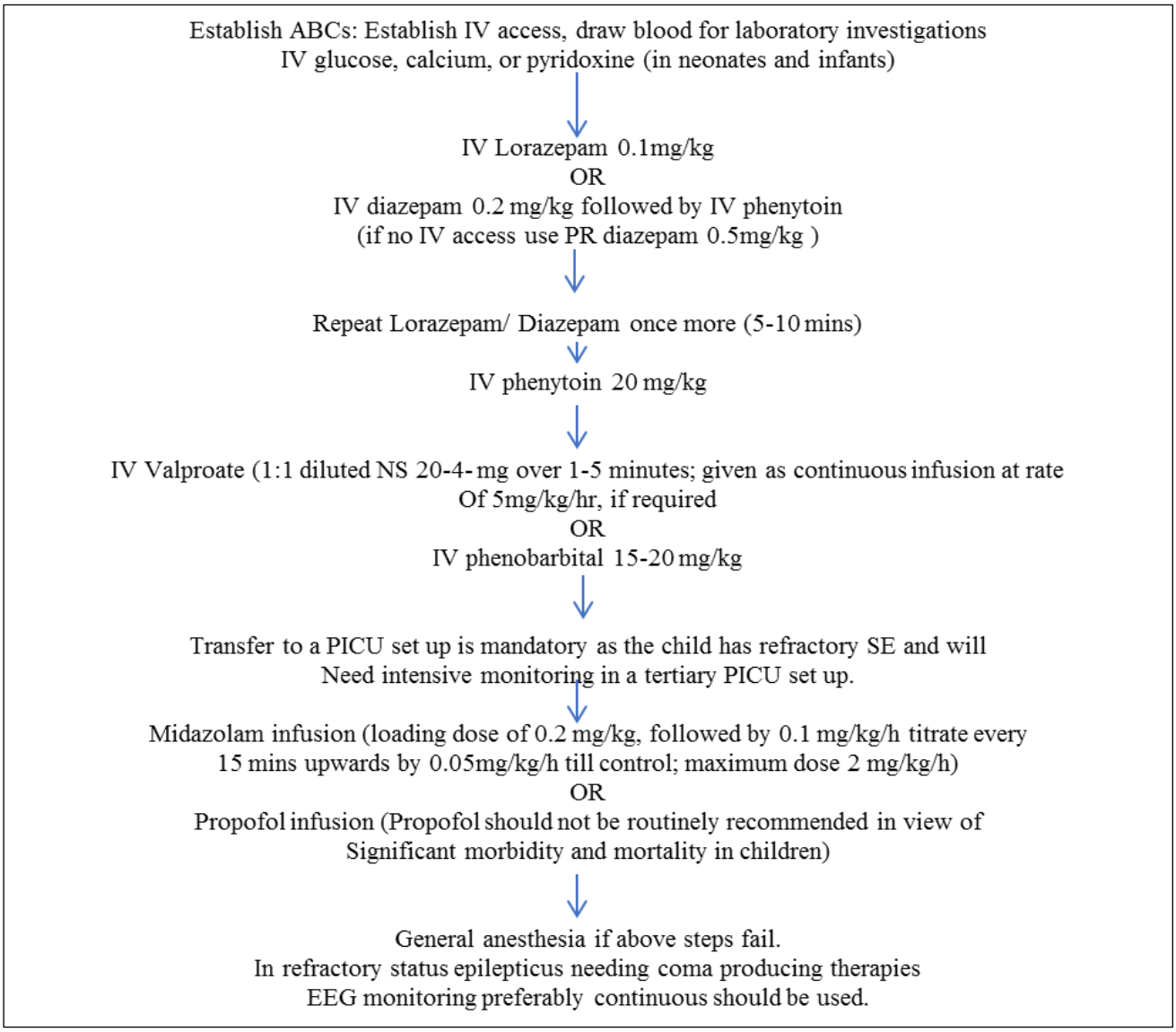

Figure 3: Management algorithm for status epilepticus.[7]

From other studies

A randomized controlled trial that tested the efficacy of the KD in children with intractable epilepsy found that 60% of patients had more than 50% seizure frequency reduction and 10% were seizure-free. Our sample population included patients (50%) with Lennox Gastaut syndrome, who are more likely to experience a reduction in seizure frequency when receiving KD treatment. From Sampaio et al study, it can be seen that after three months, the responder rate (more than 50% seizure frequency reduction) was 6/10 (60%) and 10% of patients were seizure-free.[10] According to Neal et al, their RCT on 145 children with refractory seizures shows that after 3 months, the mean percentage of baseline seizures was significantly lower in the diet group than in the controls (62.0% vs 136.9%, 75% decrease, 95% CI 42.4–107.4%, p <0.0001). 28 children (38%) in the diet group had >50% seizure reduction compared with four (6%) controls (p <0.0001), and five children (7%) in the diet group had greater than 90% seizure reduction compared with no controls (p=0.0582).[11] And according to Lamberechts et al, their RCT shows that KD is an effective therapy in children and adolescents with refractory epilepsy compared with care as usual.[12,13]

Types of ketogenic diet

Multiple variations of ketogenic diets exist, but the most commonly prescribed are the classic KD, the modified Atkins diet, the low-glycemic index treatment diet, the medium-chain triglyceride (MCT) diet, and the modified MCT diet. They were summarized in Table 3 and Table 4.[9]

Table 2: Anti-epileptic drug.[7]

Name	Usage	Dosage (Mg/Kg/Day)	Side effect
Phenobarbitone	First line in neonatal seizures in the first two years of life for partial seizures and early infantile status epilepticus (SE)	3-6 (single night-time dose) 20 mg/kg (loading dose for SE)	Deleterious cognitive and behavioral
Phenytoin	Should not be preffered as primary AED ir newly diagnosed epilepsy	Older children: 5-6 (once or twice daily) Infants: 15-18 (3-4 divided dose)	Poor seizure control fluctuating drug level, gum hyperplasia, hirsutism
Valproate	• Broad spectrum efficacy • Drug of Choice (DOC) for newly diagnosed epilepsy	10-40 (twice daily)	Weight gain, hair loss, aggravation of polycystic ovarian disease (PCOD)
Carbamazepine	• First choice for newly diagnosed partial epilepsies after the age of 2 years. • Focal, CTG and mixed types seizures • Exacerbates myoclonic and absence seizure	10-30 (twice daily)	Ataxia, diplopia, rash, school performance worsening Appearance of new seizures
Ethosuximide	Absence epilepsy	20-30 twice daily	Abdominal discomfort, hiccups, headaches, sedation
Lamotrigine	• Monotherapy in focal seizures • Adjunctive therapy for seizures associated with therapy refractory Lennox Gastaut syndrome.	0.2-0.5 twice daily	Skin rash, dizziness, ataxia, SJS
Gabapentin	• Monotherapy in focal seizures • Adjunctive therapy for partial seizures	30-60 (3 times daily) (monotherapy: ≥12 years) (adjunctive: ≥3 years)	Somnolence, dizziness, ataxia. Fatigue blurred vision, diplopia, rash, aggressive behavior, weight gain.
Oxcarbazepine	Monotherapy or adjunctive for focal seizures	20-40 (twice daily)	Sedation, headache, ataxia, hyponatremia (rare)
Topiramate	• Monotherapy with new diagnosed epilepsy • Adjunctive therapy for focal seizures, primary GTC seizures, Lennox Gastaut syndrome	Initial: 0.5-1 Maintenance: 3-9	Anorexia, weight loss, begavior changes, hyperthermia, renal stone, ascidosis

Mechanism of KD as anticonvulsant

The anticonvulsant efficacy of the KD has been examined in various acute and chronic animal models of epilepsy over the years. In rodents, maximal seizure control develops 1-2 weeks after initiation of a KD. Similarly, in humans, clinical efficacy does not reach its zenith in many patients until after 2 weeks.[8]

The role of ketone bodies

There is some evidence that ketones other than BHB may possess anticonvulsant properties. When injected into animals, acetone and acetoacetate (ACA), prevent acutely provoked seizures. Recently, it has been suggested that ACA and/or its metabolic byproduct, acetone, may activate a novel class of potassium leak channels known as the two-pore domain or K2P channels.[13] K2P channels represent a diverse superfamily of channels that generally hyperpolarize cell membranes, and regulate membrane excitability both pre and postsynaptically. These channels can be modulated by changes in pH, osmolality, temperature, mechanical pressure, and certain fatty acids.[8]

β-hydroxybutyrate is the predominant blood ketone body and is oxidized to acetoacetate in the mitochondria before entering the TCA cycle. Rho and colleagues found that it was acetoacetate and acetone other than β-

hydroxybutyrate that can significantly decrease the epileptic seizures in the seizure-susceptible juvenile mouse model, indicating anticonvulsant effects of these ketone bodies. To investigate the effects of KD and anticonvulsant drug combination, Szot and his colleagues performed coadministration of valproate and ketogenic diet and examined its effect. In majority of the cases, it seemed safe to coadministrate valproate and ketogenic diet. Only in two cases, valproate made a negative influence on ketosis. Their research sheds new light on the combination strategy of KD and anticonvulsant drugs.[14]

Table 3: Types of ketogenic diet.[9]

	Macrinutrient content (% total daily calories)			Comments
	Fat	**Protein**	**Carbohydrate**	
Classic ketogenic diet	LCT: 85-90	6-8	2-4	• 4:3 or 3:1 (fat: nonfat) ratio • unpalatable= poor compliance • GI effects: constipation
MCT diet	MCT: 71	10	19	• 3:1 (fat: nonfat) ratio • Easier to prepare • Greater flexibility with protein and carbohydrate allowance • GI effects: cnausea, vomiting, diarrhea in 50% patients
Modified MCT diet	LCT: 40-5 MCT: 30	10-2-	5-10	• Incorporates LCT and MCT • Fewer GI effects
Modified Atkins diet	60-70	20-3-	5	• No fasting or hospital stay • No calore restrictions • Less dietitian support
Low-glycemic-index treatment diet	60-70	20-3-	10	• Only low glycemic index carbohydrate allowed for 10% daily carbohydrates • Details of how diet is prescribed are not widely known

Table 4: Sample calculations of daily energy requirements for the 3:1 classic ketogenic diet for 18 kg patient.[9]

Daily energy requirements
Daily caloric requirement • Total body weight x 68 cal/kg/day • 18 kg x 68 cal= 1224 cal/day

Daily number of dietary units
• For 3:1 (fat: prtoein/ carbohydrates)
  • 3 g fat/ unit x 9 cal/g fat= 27 calories
  • 1 g protein or CHO/ unit x 4 cal/ g protein or carbohydrates= 4 calories
  • 27 +4= 31 calories/ unit
• daily caloric requrement: calories/unit= dietary units/ day
  • a. 1224: 31= 39 units/ day

Daily fat content • Dietary units/ day x g fat/ unit= g fat/ day • 39 units/day x 3 g fat/unit= 117 g fat/ day
Daily protein and CHO content (combined) • Dietary units/ day x g protein or CHO/unit= g protein or CHO/ day • 39 units/ day x 1 g protein or CHO/ unit= 39 g protein and CHO/ day
Daily protein content= 1 g/kg/day • 1g/kg/day x 18 kg= 18 g/day
Daily carbohydrate content • Combined protein and cho content- daily protein content= daily carbohydrate content • 39 g protein and cho/day- 18 g protein/day= 21 g CHO/ day
Divide allotment into 3 meals • Fat= 117: 3 = 39 g/ meal • Protein 18: 3= 6 g/ meal • cho 21: 3= 7g/ meal

The effect of KD on neuron metabolism

The brain metabolizes ketone bodies for energy when glucose levels are rapidly decreased during KD. It has been established that the efficacy of the KD for managing epilepsy is best when the diet is administered following a fast or when total calories are restricted. Furthermore, the seizure protective effects of KD are found to rely on the maintenance of low blood glucose levels which force the brain to burn ketones for energy. Ketone metabolism gradually reduces neuronal excitability, thereby producing effects on neurotransmitter levels and neuron membrane potential.[15]

The effects of KD on neurotransmitter function

GABA signaling is the most well studied target of investigation since mouse models of epilepsy induced by GABA antagonists exhibited a remarkable response to KD treatment. Moreover, in rat synaptosomes GABA synthesis was greatly increased and maintained at a high level by ketone bodies, which may contribute to the beneficial effect of KD in the treatment of epilepsy. Many clinical studies showed increased GABA levels in the cerebrospinal fluid of patients on a KD, further supporting that GABA might be regulated by ketone bodies.[15]

The effect of KD on neuronal membrane

Another potential mechanism underlying the effects of ketone bodies on epileptic seizures is their effects on neuronal membrane transporters. Ketone bodies may alter the behavior of vesicular glutamate transporters (VGLUTs) that are responsible for filling presynaptic vesicles with glutamate in a Cl-dependent manner. Juge and colleagues demonstrated that Cl- is an allosteric activator of VGLUTs that is competitively inhibited by ketone bodies (acetoacetate) more strongly than β-hydroxybutyrate.

Abnormal gap junctional communication is an underlying mechanism involved in the generation and maintenance of seizures. Consequently, the effects of gap junction blockers were determined in seizure models. As a result, these gap junction blockers can reduce both amplitude and frequency of the epileptiform activity, and modify the behavioral parameters related to seizures in vivo assay. However, no clinical evidence supported the correlation between KD treatment and the gap junctional communication.[15]

Role of fatty acid on KD

PUFAs are becoming an increasingly popular focus of KD research. After KD treatment, specific PUFAs (i.e., DHA) were found to be elevated in both serum and brain of patients and animals. One report documented that the rise (or drop) in total fatty acids during KD treatment closely paralleled clinical improvement of seizure control. PUFAs could ultimately block seizure activity in a number of ways (Figure 4). First, PUFAs may inhibit directly ion channel activity. Omega-3 (ω-3) PUFAs have been shown to inhibit both voltagegated Na+ and Ca2+ channels, increase the resistance to bursting induced by bicuculline, zero Mg2+, pentylenetetrazole or glutamate, and prolong the recovery time from inactivation in hippocampal neurons. Second, in conjunction with ketone bodies, PUFAs may activate a lipid-sensitive class of K2P potassium channels. And, third, PUFAs may enhance the activity of the Na+ /K+ -ATPase (sodium pump). Elevated ω-3 and diminished ω-6 PUFAs levels in plasma membranes significantly increased sodium pump function. These findings indicate that elevations levels of PUFAs after KD treatment might act directly to limit neuronal excitability and dampen seizure activity.[8] The ketogenic diet pathways can be seen in Figure 4.

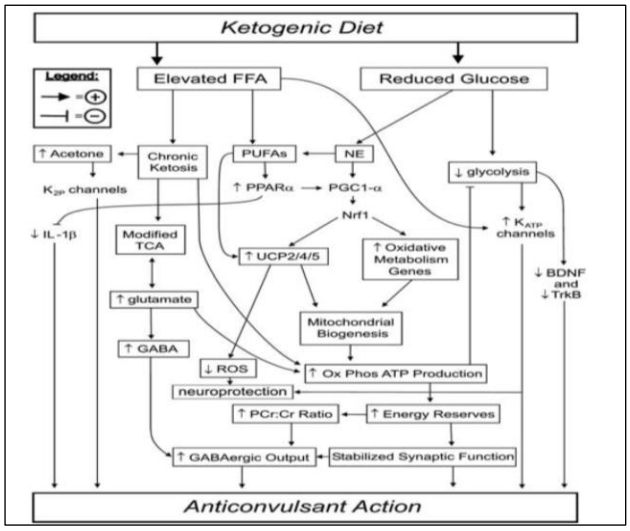

Figure 4: Ketogenic diet pathways.[8]

The role of glucose restriction

Others have hypothesized that glucose restriction during KD treatment activates ATP-sensitive potassium (KATP) channels. Interestingly, KATP channels are ligand gated receptors broadly expressed throughout the central nervous system, in both neurons and glia. These channels act as metabolic sensors, linking cellular membrane excitability to fluctuating levels of ADP and ATP. Activation of this receptor by reduced ATP/ADP ratios opens the channel and leads to membrane hyperpolarization. When glucose is limited, KATP channels might open to hyperpolarize the cell as the intracellular ATP concentrations fall. Conversely, when glucose is present and ATP concentrations rise, KATP channels close. As such, KATP channels may provide a measure of protection against a variety of metabolic stressors such as hypoxia, ischemia, and hypoglycemia, and are believed to regulate seizure threshold. Genetically engineered mice that overexpress the sulfonylurea (SUR)

subunit of KATP channels were significantly more resistant to seizures induced by kainite and showed no marked cell loss in hippocampus. Studies of KATP channel knockout mice suggested that these channels help determine seizure threshold. Following hypoxic challenge, knock out mice exhibited myoclonic-tonic seizure activity, and, ultimately, death compared to controls who all recovered without sequelae. several findings are consistent with the no- tion that KATP channels are selectively activated during administration of a low-glucose, high-fat KD.[8]

Adverse effects

The most common adverse effect of the KD is constipation. The regular inclusion of fibrous vegetables, carbohydrate- free stool softeners, mild laxatives, and sufficient fluids are helpful in maintaining bowel regularity.[1] Sampaio et al, report that in their study, the most frequently reported adverse effects were hunger, constipation, and hypoactivity.[10]

DISCUSSION

There were many randomized controlled trials on ketogenic diet for children with refractory epilepsy. One of them are Neal et al, who found that there is no significant difference in the efficacy of the treatment between symptomatic generalized or symptomatic focal syndromes. She reports the most frequent side effects were constipation, vomiting, lack of energy and hunger. Weijenberg et al, studied the ketogenic diet in liquid form and their study concludes that ketogenic diet with a liquid formulation is feasible and can be safely introduced in an outpatient setting. As from Lambrecth et al, their study result in the effective therapy in children with refractory epilepsy is with ketogenic diet rather than standard therapy and the side effects were gastrointestinal symptoms, it is the same as other studies implied. From Sampaio et al, it was said in the study that KD is effective in reducing the frequency of seizures and improving cognition and the quality of life of patients.[10]

CONCLUSION

In conclusion, this review article summarized many important aspects of pediatric epilepsy and the role of ketogenic diet in treating epilepsy. The antiepileptic efficacy of KD in epilepsy has been found to increase the number of experimental evidences and raise a promising therapeutic strategy against epilepsy. This review article shown that the diet has efficacy and should be included in the management of children who have drug-resistant epilepsy. However, the diet is not without possible side-effects, which should be considered alongside the risk-benefit of other treatments when planning the management of such children.

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