Practical Use of the Ketogenic Diet in Childhood Epilepsy

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1. Introduction

The ketogenic diet (KD) is a high fat, low carbohydrate diet that has been used for intractable childhood epilepsy since the early 1920s. After the resurgence of the ketogenic diet in the mid 1990s, it has been used worldwide for the treatment of refractory pediatric epilepsy. Thus the ketogenic diet is an established, effective nonpharmacologic treatment for intractable childhood epilepsy. Over the past decade the role of the ketogenic diet in the treatment of intractable epilepsy has become evident from the explosion of interest and publications available, as well as the increased number of epilepsy centers that offer the ketogenic diet. However, the ketogenic diet is not yet a convenient therapy, especially because the customary diets of Asian countries contain substantially less fat than the traditional Western diets. Therefore, recent research endeavor to achieve a safer and more convenient dietary treatment for refractory pediatric epilepsy.

Recent consensus of ketogenic diet by expert’s opinion provided guideline in using the diet. Suggested protocols, which include changes to the applicable ages, seizure types, and etiologies, the initiation of the diet, changes in the ratio of constituents to reduce the fat content, the duration of the diet, and revised formulae, such as ketogenic milk or the all-liquid ketogenic diet, have attempted to extend the indications of the ketogenic diet and increase its tolerability. Physicians should also be aware of the various complications of the diet. Less restrictive ketogenic diet including a modified Atkins and low-glycemic-index diets have also been clinically tried with comparable efficacies.

This chapter will provide practical recommendations to guide the management of the ketogenic diet in childhood epilepsy and give a review on the current state of ketogenic diet.

2. Background

Epilepsy is the most common serious neurological condition in the world, with an estimated prevalence of 1\% of the population. Traditional epilepsy management includes pharmacological treatment, epilepsy surgery, and vagal nerve stimulation. Despite these therapies, 25\% of children continue to have uncontrolled seizures. The ketogenic diet, which has been in use since 1921, is a treatment option for many of these children. The original
classical ketogenic diet is based on a ratio of fat to carbohydrate and protein, usually 3:1 or 4:1. Protein is kept to minimum requirements for growth, and carbohydrate sources are mostly limited to small portions of vegetables or fruit. The classic diet is calculated using a ratio of the weight of fat to the sum of protein and carbohydrate. Protein is provided to meet dietary reference intake, which is approximately 1 g per kilogram of body weight. Carbohydrate completes the remaining allowance of the ratio. Although it is a “ketogenic diet,” one nutrient class (carbohydrates) is depleted, while providing an alternative fuel source for the brain with another substrate (ketones), which may be anticonvulsant.

Ketogenic diets are categorized as either long-chain fatty acid based or medium-chain fatty acid based. The classical ketogenic diet uses long-chain triglycerides (LCT). Medium-chain triglycerides (MCT) are more ketogenic than LCTs, as octanoic and decanoic acids are more easily transported into the cell (Huttenlocher, 1976). Since it is more ketogenic, the MCT ketogenic diet (MCT-KD) allows for a lower overall fat content and subsequent greater inclusion of protein and carbohydrate in the daily intake (Sinha & Kossoff, 2005). Clinically, there does not appear to be a difference in efficacy between the MCT and the LCT diets (Huttenlocher et al., 1971; Schwartz et al., 1989). Patients on the MCT diet are more likely to experience abdominal bloating and diarrhea than those on the LCT diet, which is believed by some, in return, to be less palatable than the MCT diet. In addition, patients on the LCT diet are more prone to constipation than those consuming an MCT diet (Hartman & Vining, 2007). Other options have been devised for using the diet in particular situations, such as in patients fed through a gastrostomy tube or in infants. These diets include ketogenic diet formulas of the Nutricia’s (MD, USA) KetoCal®, Solace Nutrition’s (MD, USA) KetoVolve® and Ketonia™ in South Korea. The availability of these formulas for infants, particularly those with gastrostomy tubes, makes palatability less of a problem in this patient population (Sinha & Kossoff, 2005). For infants with epileptic encephalopathy and infantile spasms, a short-term trial of the diet for about 6-12 months, including a 2-4 month tapering-off period, can be considered (Kang et al., 2011).

The ketogenic diet is an effective treatment for medically refractory epilepsy, and is characterized by elevations in ketone bodies and fatty acids in both blood and brain. While a detailed understanding of the anticonvulsant mechanisms of action of the ketogenic diet has remained elusive, recent investigations have suggested that a global shift from glycolysis to fatty acid oxidation is necessary to achieve the desired clinical effects. Moreover, there are growing data indicating that the ketogenic diet – whether through ketone bodies or PUFAs – can exert neuroprotective actions, most likely by enhancing ATP production and decreasing ROS production, both of which help to preserve mitochondrial integrity. Also there is growing evidence that the ketogenic diet alters the fundamental biochemistry of neurons in a manner that not only inhibits neuronal hyperexcitability but also induces a protective effect (Kim do & Rho, 2008).

3. The history of the ketogenic diet

Fasting has been used in the treatment of epilepsy since Biblical times (Matthew 17:5-21). To mimic the metabolism of fasting, the ketogenic diet was introduced by modern physicians as a treatment for epilepsy in the 1920s (Geyelin, 1921). Wilder (Wilder, 1921) postulated that the antiepileptic effect of the diet was related to the production of ketones and not to starvation. He proposed that increasing the fat content in the diet while reducing the
carbohydrate would lead to reduction in seizure frequency. In the following decades, the use of the ketogenic diet were eclipsed as phenytoin, and then other anticonvulsants, became available in the late 1930s. With the development of newer antiepileptic drugs with improved efficacy and convenience, there was a significant decrease in the use of the ketogenic diet. However, the varied adverse effects of such medications should be considered, especially since more than 25% of epilepsy remains intractable, despite the development of new anticonvulsants (Kwan & Brodie, 2000).

The diet regained widespread recognition as a viable treatment option beginning in 1992 due to the efforts of parent advocate groups. This changed dramatically when the ketogenic diet received national media attention via NBC-TV’s Dateline program on the treatment. This television program was based on the true story of Charlie, a 2-year-old boy with intractable generalized seizures, who presented out of desperation to Johns Hopkins Hospital for treatment. He was seen by Dr. Freeman and Ms. Millicent Kelly (the same dietitian who had worked with Dr. Livingston) and initiated on the ketogenic diet. He quickly became seizure-free and the Charlie Foundation was formed by his father. He made videos for parents, physicians, and dietitians about the ketogenic diet. In addition, he directed the movie First Do No Harm, starring Meryl Streep, in 1997, which presented the ketogenic diet as a miracle cure for epilepsy. This exposure to the diet in the popular media contributed to a movement led by patients and their families to expand use of the treatment (Bailey et al., 2005). The Foundation also supported the first multicenter prospective study of the efficacy of the ketogenic diet (Vining et al., 1998). There has been an explosion in both the use, and scientific interest in the ketogenic diet. The ketogenic diet has experienced a reemergence in recent years and modern clinical studies have established the treatment as significantly effective (Freeman et al., 1998). The ketogenic diet is now available in over 45 countries (Kossoff & McGrogan, 2005).

4. Efficacy and complications of the ketogenic diet

To establish the efficacy of the ketogenic diet, this procedure requires the development of a blinded prospective study using a well-defined cohort and sufficient sample size (i.e., Class One Evidence). To date, no studies met the criteria for Class One Evidence for efficacy in the use of ketogenic diet in children with refractory epilepsy. The development of a blinded prospective trial of the ketogenic diet in children would be difficult to design (Thiele, 2003). Finding a placebo with similar metabolic responses to the diet both at the time of initiation (i.e., acidosis, lethargy, hypoglycemia) and during the maintenance phase (presence of ketones) that does not have antiepileptic properties would be difficult. Therefore, the diet’s efficacy has been established primarily through large case series. Many reports on the efficacy of the ketogenic diet have shown similar outcomes. After 12 months on the ketogenic diet, about 50% of patients remained on the diet, 30%-70% of patients showed a reduction in seizure frequency of more than 50%, and 10%-20% were seizure-free(Kang et al., 2005). Recent papers (Keene, 2006) reported an overall reduction of seizure frequency greater than 50% in approximately one third of children initiated on the diet. The duration the child remained on the diet was variable, with over half the children discontinuing the diet between 6 months and a year after the treatment onset. Although the efficacy of the ketogenic diet is not maintained in all patients after they discontinue the diet, beneficial effects persist in most patients relative to their symptoms prior to diet initiation(Hemingway et al., 2001; Kang et al., 2005). Because of the variation in study designs and in the
description of the clinical variables (such as seizure type, electroencephalographic findings, duration of treatment), it was not possible to assess which child might benefit most from the diet (Keene, 2006). The widespread acceptance of the ketogenic diet has ended the debate about its efficacy.

The ketogenic diet predisposes to nutritional deficits in energy, proteins, minerals, and vitamins and excess in lipids, saturated fat, and cholesterol. Use of such an unbalanced diet requires particular attention regarding its implementation and monitoring, particularly in children. Some adverse events may occur within a few days or a month of commencing the diet, although others may occur after several months (table 1)(Freeman et al., 2006; Kang et al., 2004; Lyczkowski et al., 2005). The potentially serious complications should also be considered. Rare, life-threatening complications, such as cardiomyopathy, serious infections, or aspiration pneumonia leading to respiratory distress, should be carefully monitored for during follow-up (Kang et al., 2004). Especially in patients with cardiac arrhythmias such as prolonged QT interval (Best et al., 2000), and in patients with underlying metabolic disorders or those taking zonisamide, topiramate, or acetazolamide (Kossoff et al., 2002; Takeoka et al., 2002), the use of the diet might be associated with a higher risk of adverse events. However, most events are transient or can be controlled with regularly scheduled assessments (table 2) and conservative management.

<table>
<thead>
<tr>
<th>Early- and late-onset</th>
<th>Late-onset</th>
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<tr>
<td>Gastrointestinal disturbances*</td>
<td>Growth retardation</td>
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<tr>
<td>Dehydration†</td>
<td>Hepatic failure</td>
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<tr>
<td>Infectious disease‡</td>
<td>Exacerbation of gastro-esophageal reflux</td>
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<tr>
<td>Sepsis</td>
<td>Mineral deficiencies</td>
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<td>Lipoid aspiration pneumonia</td>
<td>Vitamin deficiencies</td>
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<tr>
<td>Hepatitis</td>
<td>Osteopenia</td>
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<td>Acute pancreatitis</td>
<td>Renal stone</td>
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<tr>
<td>Biochemical disturbances</td>
<td>Cardiomyopathy</td>
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<tr>
<td>Abnormal lipid profiles§</td>
<td>Prolonged Q-T interval</td>
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<tr>
<td>Symptomatic hypoglycemiaΠ</td>
<td>Iron deficiency anemia</td>
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<td>Persistent metabolic acidosis</td>
<td>2nary hypocarnitinemia</td>
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<td>Hypoproteinemia</td>
<td>Optic neuropathy</td>
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<tr>
<td>Repeated hyponatremia</td>
<td>Basal ganglia injury</td>
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<td>Hyperuricemia</td>
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(*) Nausea/vomiting, diarrhea, constipation, loss of appetite. (†) A body weight reduction of over 5% of the baseline and marked dry skin or mucous turgor with increased urine specific gravity of over 1.020. (‡) Pneumonia, cystitis, nonspecific febrile illness. (§) High triglyceridemia, high cholesteroloma, low high density lipoproteinemia. (Π) <40 mg% of blood sugar with nausea, lethargy, perspiration, dizziness, tachycardia and pale appearance. (Adapted from Dr. Kang HC).

Table 1. Early- and late-onset complications of the ketogenic diet.

5. Protocol of the classic ketogenic diet

While the Hopkins protocol has been the basic model, the general protocol has evolved over time, as new advances have been made in how the diet is administered and followed (Kang & Kim, 2006). Prior to introducing the ketogenic diet, patients are screened by history and
exam (as well as supporting laboratory studies, if indicated) for metabolic disorders that may affect their ability to generate adequate amounts of ketones. A brief hospitalization for 3-7 days was also recommended to give parents and children extensive instructions on how to calculate and prepare the diet, identify potential sources of glucose, and address other possible sources of error in administering the diet. On the first day of feeding, the patient is given 1/3 of the planned total caloric intake; on the second day, 2/3 of the total calories are administered, and on day 3, the full (previously calculated) caloric intake is administered. While on the diet, patients should also receive recommended daily intakes of vitamins and minerals (in sugar-free formulations), as well as calcium supplementation, as the ketogenic diet is not nutritionally complete. During the diet’s initiation, blood glucose, urine ketones, and vital signs are monitored. The outpatient phase of the ketogenic diet consists of routine clinic visits (3, 6, 12, 18, and 24 months after starting the diet) with the staff and laboratory measurements, along with frequent contact with the nutritionist (table 2).

<table>
<thead>
<tr>
<th>Pre-diet</th>
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<tr>
<td>Metabolic workups* (lactate, urine organic acid and plasma acylcarnitine profiles) urine ALA and PBG†</td>
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<tr>
<td>0,1,2,3,4 days and monthly</td>
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<tr>
<td>Blood ketone, blood sugar (every 12 hours for 4 days)</td>
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<tr>
<td>0,3 days and 1,3,6,12,18,24 months</td>
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<tr>
<td>CBC with platelets, BUN/creatinine, liver profiles‡, electrolytes with tCO2, calcium/phosphorus/alkaline phosphatase, magnesium, uric acid, lipid profiles§, urinalysis, PT/PTT, urine ca/urine creatinine</td>
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<tr>
<td>0,6,12,24 months</td>
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<tr>
<td>Blood AED levels, abdominal ultrasonography, echocardiography</td>
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<tr>
<td>plain X-ray on wrist, if needed, bone densitometry, bone enzyme profilesΠ</td>
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<tr>
<td>Intermittently</td>
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<td>Urine ketone¶</td>
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ALA = d-aminolevulinic acid; PBG = porphobilinogen; CBC = complete blood count; BUN = blood urea nitrogen; PT = prothrombin time; PTT = partial thromboplastin time; AED = antiepileptic drug. (*) In children with associated developmental delay of unknown etiology, hypotonia, exercise intolerance, cyclic vomiting, fatigability, hepatomegaly, cardiomyopathy, pigmentary retinitis, hypoaucia, metabolic acidosis, hypoglycemia, hyperammonemia or unexpected ketonuria. (†) Especially in nationalities that have high incidence of acute intermittent porphyria. (‡) Total protein/albumin, total bilirubin, aspartate aminotransferase and alanine aminotransferase. (§) Cholesterol, high density lipoprotein-cholesterol, triglyceride. (P) Parathyroid hormone, 25(OH) vitamin D3, 1,25(OH)2 vitaminD3, osteocalcin. (¶) Recommend measurement of urine ketones at home, especially when seizures occur or seizure frequencies increase. (Adapted and revised from Dr. Kang HC)

There is the need for standardized protocols and management recommendations for both clinical and research use of the diet, because the ketogenic diet is provided differently throughout the world, with occasionally significant variations in its administration. In December 2006, the Charlie Foundation commissioned an international committee of neurologists and dietitians with expertise in the ketogenic diet. The charge of this consensus group was to provide practical recommendations to guide management of the ketogenic diet (Kossoff et al., 2009). Recommendations are as follows:
Patient selection
The ketogenic diet should be strongly considered in a child who has failed two to three anticonvulsant therapies, regardless of age or gender, and particularly in those with symptomatic generalized epilepsies. The ketogenic diet yielded a good response in patients with an immature cerebral cortex due to developmental malformation (Jung et al., 2008b). It can be considered the treatment of choice for two distinct disorders of the brain metabolism, i.e. the GLUT-1 deficiency syndrome and PDHD. In particular epilepsy syndromes, such as the Dravet syndrome, infantile spasms, myoclonic-astatic epilepsy, and tuberous sclerosis complex, the ketogenic diet could be offered earlier. Before starting the ketogenic diet, inborn errors of metabolism that could lead to a severe metabolic crisis should be ruled out. For example, defects in fatty acid oxidation generally are contraindications to starting the ketogenic diet. Absolute contraindications to the ketogenic diet include pyruvate carboxylase deficiency and porphyria.

Medications and the ketogenic diet
There is little evidence of any consistent positive interactions between the ketogenic diet and anticonvulsants. The ketogenic diet may work well in combination with VNS. Conversely, the ketogenic diet is not negatively affected in regards to efficacy or side effects by any particular anticonvulsant. Medications can often be reduced within the first few months if the ketogenic diet is successful, although caution is advised especially when reducing phenobarbital and benzodiazepines.

Maintenance of children receiving the ketogenic diet
Ongoing clinic visits at least every 3 months for the first year, with ready access to experienced advice, are important for the successful management of children receiving the ketogenic diet. More frequent visits may be necessary for infants and other patients at high risk for nutritional deficiency. All children should be seen by experienced pediatric neurologists and dietitians and should have a nutritional assessment, laboratory evaluation, and discussion regarding ketogenic diet and anticonvulsant discontinuation decisions.

Ketogenic diet discontinuation
Consideration should be given to discontinue the ketogenic diet after 3 months if unsuccessful, or after 2 years if completely successful. However, longer diet durations are usually necessary for GLUT-1 and PDHD and may be perfectly appropriate, based on individual responses for intractable epilepsy. Prior to diet discontinuation in seizure-free children, a routine EEG and review of clinical data should be performed to counsel families regarding recurrence risk, which is 20% overall. Children with an epileptiform EEG, abnormal MRI, and tuberous sclerosis complex are at higher risk. During discontinuation, the group generally recommends a gradual wean over 2–3 months, as outlined above, unless an urgent discontinuation of the diet is indicated.

6. Newer versions of the diet
In Asia, even now, the ketogenic diet is still not convenient to use, especially because the customary diets of Asian countries contain substantially less fat than traditional Western diets. Moreover, in adolescents, an unpalatable diet may cause resistance and poor compliance and a lower ability to extract ketones from the blood into the brain can be a barrier to its effectiveness (Williamson, 1985). In addition, there are various complications associated with the diet and they should be carefully considered. Therefore, we require an
alternative diet therapy that is safer and more convenient while maintaining efficacy. In the last decade, variations to the classical ketogenic diet have been utilized. Recently less restrictive ketogenic diet, including a modified Atkins diet and low-glycemic-index treatment, has been suggested to replace the conventional ketogenic diet (Kossoff et al., 2006; Pfeifer & Thiele, 2005). Modified Atkins diet (grams of fat: protein and carbohydrate, 1:1 ratio) has several advantages over the traditional ketogenic diet, most notably no restriction on protein, calories, or fluids. This “Modified Atkins Diet” restricts only carbohydrates to 10 g/day (15 g/day in adults) while encouraging high fat foods. The antiepileptic effects of both fasting and the ketogenic diet have been associated with decreased blood glucose and increased blood ketone levels (Owen et al., 1967); however, recent research indicates that ketosis alone cannot account for the anticonvulsant effects of the ketogenic diet (Greene et al., 2003); it suggests that regulation of blood glucose may be at least partly responsible for these effects. The glycemic index describes the tendency of foods to elevate blood glucose (Jenkins et al., 1981). The glycemic index is calculated from the incremental area under the blood glucose curve after feeding, indexed to ingested glucose = 100. Foods with high glycemic index (e.g., most refined carbohydrates) produce substantial increases in blood glucose and insulin levels, whereas foods with a low glycemic index (e.g., meat, dairy, some fruits, some vegetables, and some unprocessed whole-grain foods) induce lower postprandial plasma glucose and insulin profiles. By limiting the quantity of carbohydrates consumed and by restricting sources of carbohydrates to low-glycemic index foods, the low glycemic index treatment (LGIT) is designed to prevent dramatic postprandial increases in the blood glucose (Pfeifer & Thiele, 2005). The low glycemic index treatment, compared to the ketogenic diet, allows for a more liberal total carbohydrate intake but restricts foods to those that produce relatively little elevation in the blood glucose (i.e. glycemic index <50). In conclusion, modification of the ketogenic diet with higher carbohydrate/protein and lower fat than the classic ketogenic diet, such as the modified Atkins diet or the low-glycemic-index treatment, can be used with similar efficacy and better tolerability (Carrette et al., 2008; Ito et al., 2008; Kang et al., 2007; Kossoff et al., 2003; Kossoff et al., 2006; Kossoff et al., 2008; Kossoff et al., 2007; Muzykewicz et al., 2009).

7. How to provide a successful ketogenic diet

As current thinking focuses on making the ketogenic diet safer and more palatable, the original protocol has been modified and has evolved to achieve increased efficacy and tolerability (Kang & Kim, 2006). Improving and maintaining efficacy is a major goal in the use of the ketogenic diet. Comprehensive dietary education and an easy calculation method, using a software program based on accurate food composition analysis, are important to use the ketogenic diet in an optimal fashion. The calculation of a single meal can be tedious, and hence the possibility for errors is significant. Computer applications for calculating ketogenic diet, such as KetoCalculator (Zupec-Kania, 2008), are available and can save time and minimize errors. The presence of well trained dietitians is critical and they should instruct caregivers in both dietary calculation and food composition. The dietitian provides nutrition management and technical manipulation of the diet in order to optimize the seizure control. The dietitian is frequently communication with both the caregivers and the ketogenic diet team, and this necessitates his/her role as coordinator of the ketogenic diet program. Dietary education also plays an important role in increasing the efficacy of the ketogenic diet. Key members of the team managing the patient include physicians, nutritionists familiar with the diet, nursing staff, and, most importantly, patients and their families. Families should be encouraged to
participate in support groups to share information and build strong bonds; this, in turn, will increase the maintenance rate of the diet.

To improve the antiepileptic efficacy of the ketogenic diet, the maintenance of consistent and strong ketosis is important. Furthermore, the lipid:nonlipid ratio affects the efficacy, as seen in many animal studies and one clinical study (Seo et al., 2007). When a child on the ketogenic diet does not show a significant reduction in seizure frequency, physicians should consider every possible way in which ketosis may be breached. It is important to maintain an accurate lipid:nonlipid ratio for each of the patient's meals and to avoid extra carbohydrate consumption derived from prescribed drugs or miscalculation.

Improving tolerability is the other major arm for the successful maintenance of the diet. Although the Johns Hopkins protocol used for the classic ketogenic diet recommends an initial fasting period, a nonfasting protocol provides better tolerance in the initial period of the diet and avoids dehydration from fluid restriction (Bergqvist et al., 2005; Kim et al., 2004). It can also decrease the incidence of early complications, such as acute renal failure, elevation of blood urea nitrogen, and electrolyte imbalance. The nonfasting ketogenic diet has similar antiepileptic efficacy to the conventional fasting ketogenic diet with the additional advantage of fewer days of hospitalization. The careful monitoring of complications and their prevention and management are also valuable ways to improve patient's tolerability during the diet's maintenance. Gastrointestinal symptoms, including nausea, vomiting, diarrhea, and/or constipation, which are common early complications, may cause both the parents and patients to consider giving up the diet. Temporary use of antacids or antiemetics can help to relieve the symptoms (Jung et al., 2008a). Psychological support is also critical for families, as is education about complications and their prevention and management. To ensure successful maintenance, care-givers should have a positive attitude about the diet. The positive attitudes of doctors and parents seem to be the most important supporting factor in maintaining the diet. Although the typical ratio of fats to carbohydrates and protein (in terms of grams) is 4:1, lower ratios are used successfully in other parts of the world, such as Asia, where rice is a major dietary staple (Kossoff & McGrogan, 2005). Moreover, breaking with tradition and convincing the physicians and their patients are the most important factors to introduce the diet in Asian countries (Seo & Kim, 2008).

8. Conclusion

The ketogenic diet is a useful therapy for patients with intractable epilepsy, including some of the catastrophic epilepsies in infancy and childhood. This chapter is a review of previous and current papers regarding the proposed practical use of the ketogenic diet in epileptic children. The diet’s strictness, lack of palatability, and side effects limit its use and adversely affect both patients’ compliance and clinical efficacy. Careful planning and monitoring from a committed and experienced medical team will help ensure a successful ketogenic diet program. We should continue our endeavors to develop a safer and more convenient diet therapy that can be extended to more patients with refractory epilepsy.

9. References


Epilepsy is a neurological condition that accompanies mankind probably since its inception. About 400 years before Christ, the disease was already known by Hippocrates, who wrote the book “On The Sacred Disease”. Classically, epilepsy has been defined as a chronic condition characterized by an enduring propensity to generate seizures, which are paroxysmal occurring episodes of abnormal excessive or synchronous neuronal activity in the brain. Out of all brain disorders, epilepsy is the one that offers a unique opportunity to understand normal brain functions as derived from excessive dysfunction of neuronal circuits, because the symptoms of epileptic seizures are not the result of usual loss of function that accompanies many disease that affect the brain. I am therefore extremely honoured to present this book. The 15 very interesting chapters of the book cover various fields in epileptology â€“ they encompass the etiology and pathogenesis of the disease, clinical presentation with special attention to the epileptic syndromes of childhood, principles of medical management, surgical approaches, as well as social aspects of the disease.

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