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The use of ketogenic diet in special situations: expanding use in intractable epilepsy and other neurologic disorders

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The ketogenic diet has been widely used and proved to be effective for intractable epilepsy. Although the mechanisms underlying its antiepileptic effects remain to be proven, there are increasing experimental evidences for its neuroprotective effects along with many researches about expanding use of the diet in other neurologic disorders. The first success was reported in glucose transporter type 1 deficiency syndrome, in which the diet served as an alternative metabolic source. Many neurologic disorders share some of the common pathologic mechanisms such as mitochondrial dysfunction, altered neurotransmitter function and synaptic transmission, or abnormal regulation of reactive oxygen species, and the role of the ketogenic diet has been postulated in these mechanisms. In this article, we introduce an overview about the expanding use and emerging trials of the ketogenic diet in various neurologic disorders excluding intractable epilepsy and provide explanations of the mechanisms in that usage.

Key words: Ketogenic diet, Metabolic diseases, Epilepsy

Introduction

The ketogenic diet was first introduced in the 1920s from the observation that starvation resulted in a decrease of seizure frequency[1]. The diet became less popular after the appearance of antiepileptic drugs such as diphenylhydantoin and phenobarbital. However, the ketogenic diet reappeared after one of well-known broadcasting company aired a program on the treatment of epilepsy using it[1]. Since then, many researches have proven the efficacy of the ketogenic diet in intractable epilepsy of adults and pediatric patients including infants[2-6].

There have been several hypotheses about the mechanisms of antiepileptic effects by the ketogenic diet and some are described as follows[7-10]: the ketogenic diet alters the energy metabolism in the brain, therefore altering brain excitability; it leads to changes in cell (neuronal and perhaps glial) properties thereby reducing excitability; it enhances alterations in synaptic transmission; it is associated with changes in a variety of circulating factors which act as neuromodulators that can regulate central nervous system excitability; and it alters the extracellular environment of the brain, which helps to decrease the neuronal excitability and synchrony[10].

The main stream of those proposed mechanisms of ketogenic diet is that it changes the normal metabolism of neurons, resulting in varying neuronal excitability and plasticity, as well as modifying

neural circuits and cellular properties to enhance and normalize neuronal function. From this point of view, the ketogenic diet can be applied to various neurologic disorders other than epilepsy. An alternative use of the ketogenic diet has been tried in various conditions (Table 1). This review will cover the areas of established evidence and dietary treatments in neurologic disorders other than epilepsy and summarize the clinical researches to date.

Use of ketogenic diet in metabolic disorders

The ketogenic diet has been used in various metabolic disorders[9,11,12]. The most strongly suggested mechanism of action is providing an alternative method for some metabolic disorders such as glucose transporter type 1 (GLUT1) deficiency syndrome and pyruvate dehydrogenase complex (PDHC) deficiency[9,11]. Also, another possible explanation is that the ketogenic diet reduces oxidative stress induced by reactive oxygen and nitrogen species. One example is that the diet activates an adaptive pathway by enhancing the glutathione antioxidant system via a protective transcription factor, NF E2-related factor 2[13].

1. GLUT1 deficiency syndrome

GLUT1 deficiency syndrome (OMIM #606777) is a disease of cerebral energy metabolism caused by impaired GLUT1 mediated glucose transport into the brain[14]. It was first reported from the observation of low cerebrospinal glucose concentration (hypoglycorrhachia) with low cerebrospinal fluid lactate and normoglycemia as the diagnostic criteria. GLUT1 deficiency syndrome is characterized by an infantile-onset epileptic encephalopathy, mental retardation, deceleration of head growth, acquired microcephaly, incoordination, and spasticity. A defect in glucose transport across the blood-brain barrier is the major pathomechanism[15,16].

Currently, the ketogenic diet is regarded as the sole treatment method. The concept of maintaining ketosis in GLUT1 deficiency syndrome is clear in the treatment of the disease; the early restoration of brain energy metabolism by supplying ketones as an alternative fuel benefits both the seizure control and development[17]. Brain energy metabolism is unique especially in infancy when 80% of glucose is consumed by the brain. Additionally, the ability of the brain to extract and utilize ketone bodies in infancy is four times higher than in adults and the effect of the ketogenic diet is most effective between 2 to 5 years of age[17,18]. In one prospective study, fifteen patients with GLUT1 deficiency syndrome were treated with the ketogenic diet for 2 to 5.5 years. As a result, two-thirds of the patients who were on the ketogenic diet without antiepileptic drugs were found seizure-free. The others showed remarkable seizure reduction with add-on drugs. There were no serious adverse effects, and the parental satisfaction with the ketogenic diet was high[19]. There have been continuing reports about the successful use of the ketogenic diet or modified Atkins diet in the treatment of GLUT1 deficiency syndrome[20-22].

Table 1. Expanding Use of the Ketogenic Diet in Various Conditions

Disease
Epilepsy
Intractable epilepsy
Super-refractory status epilepticus
Dravet syndrome
Myoclonic astatic epilepsy
Metabolic disorders
Glucose transporter type 1 deficiency
Pyruvate dehydrogenase complex deficiency
Phosphofructokinase deficiency
McArdle disease
Neurologic disorders
Alzheimer disease
Parkinson's disease
Amyotrophic lateral sclerosis
Traumatic brain injury
Autism
Depression
Migraine
Other disease
Cancer

2. PDHC deficiency

Mitochondrial PDHC catalyzes the rate-limiting step in the aerobic glucose oxidation and it comprises multiple copies of three enzymatic subunits: pyruvate dehydrogenase (E1), dihydrolipoamide transacetylase (E2), and dihydrolipoamide dehydrogenase (E3), as well as an E3 binding protein. Patients with PDHC deficiency manifest poor feeding, lethargy, and tachypnea in early infancy, developmental delay, growth retardation, intractable seizures, ataxia, episodic dystonia, and abnormal eye movements[23]. Although there have been no controlled trials that have prospectively evaluated the ketogenic diet in the treatment of PDHC deficiency, there have been several case reports with some success[23-25]. The use of the ketogenic diet bypasses the metabolic block, by providing a direct source of acetyl-CoA, leading to amelioration of some symptoms[23].

3. Mitochondrial disorders

There has been increasing evidence showing that the ketogenic diet enhances mitochondrial functioning and biogenesis[9,26,27]. During

short-term fasting, the ratio of glucose to ketones in the brain can shift to 70:30, and during prolonged starvation, it may shift to 30:70. During the ketogenic diet, the brain utilizes the ketone body as a major fuel and this reduces oxidative stress and increases antioxidant enzymes[28]. This is the result of shifting of metabolism from the glucose-based state to a more fatty acid oxidation-based mitochondrial metabolism[28,29]. According to a previous study, the ketogenic diet was safe and effective in 14 pediatric patients with mitochondrial defect in complexes I, II, and IV, all of whom had intractable epilepsy[30]. In that study, half of the patients became seizure-free with the ketogenic diet. However, the ketogenic diet is not recommended for patients with primary carnitine deficiencies including carnitine palmitoyl transferase deficiencies I or II and mitochondrial translocase and fatty acid beta-oxidation abnormalities[9,31]. The reason for this is that the defect of those enzymes prevents introducing the fatty acid into the mitochondria.

4. Other metabolic disorders

The use of the ketogenic diet was demonstrated in other rare metabolic disorders. One is phosphofructokinase deficiency. Phosphofructokinase is the rate limiting enzyme in glycolysis for the conversion of fructose-6-phosphate to fructose-1, 6-bisphosphate. There was one case report, in which the patient with phosphofructokinase deficiency showed a marked gain in muscle strength and improvement in development after treatment with the ketogenic diet[11,32]. Another example is glycogenosis type V (McArdle disease) which is caused by a defect in the muscle-specific isoenzyme of glycogen phosphorylase. In healthy individuals, glycogen gets decomposed into glucose for use as a fuel in muscles. When the ketogenic diet was applied to a patient with the disorder, providing an alternative source of energy production, the patient's exercise tolerance improved[11,33].

Use of ketogenic diet in epilepsy for expanding uses

There has been a great amount of evidence that the ketogenic diet is effective in various intractable epilepsy syndromes. Recently, some studies proposed the proofs for the treatment of specific intractable epilepsy syndromes such as Dravet syndrome, myoclonic astatic epilepsy (MAE), and refractory status epilepticus[34-37].

1. Dravet syndrome

Dravet syndrome (OMIM #607208) is an infantile-onset catastrophic epilepsy and its prevalence is estimated at about 1 in 20,000 to 40,000 children with male preponderance[38]. Patients show normal development initially and experience febrile and afebrile generalized tonic-clonic seizures before one year of age. Some patients manifest various type of seizures; focal, absence, and myoclonus. Additionally, they show developmental delay, ataxia, and recurrent status epilepticus[38]. Dravet syndrome is due to genetic defect in the *SCN1A, SCN2A, SCN9A* and *GABRG2* genes[39].

The first large study using the ketogenic diet to Dravet syndrome was reported in 2005. The study included 52 patients who met the diagnostic criteria for Dravet syndrome. Twenty patients were given the diet and thirteen continued on the diet for at least one year. There was more than 75% reduction in seizures in ten children with two who became seizure-free[40]. Other studies have also reported similar results[41,42]. A prospective study was done with 15 Dravet syndrome patients who received stiripentol, clobazam, and valproate for more than six months while being on the ketogenic diet. Ten patients showed more than 75% seizure reduction and one patient became seizure-free at three months into the study period. Five patients continued to show more than 75% seizure reduction at one year. Additionally, 56% of the patients revealed an improvement in hyperactivity and inattention and 28% of them in impulsivity and aggression[43].

2. MAE

MAE was first described by Doose et al.[44] in 1970. It is characterized by a combination of seizure types including myoclonic, myoclonic-atonic, or atonic seizures between the ages of seven months and six years. Patients also have absence, clonic, generalized tonic clonic seizures, and frequent status epilepticus and are usually refractory to medical treatments[37,45].

Several studies have provided clinical evidence for using the ketogenic diet in MAE. Oguni et al.[46] reported that myoclonic-atonic seizures stopped in 89% of the patients within 1 to 3 years while generalized tonic clonic or clonic seizures persisted. According to the study by Laux et al.[47], seven of ten patients with MAE showed excellent outcome of being seizure free or >90% seizure reduction with the ketogenic diet[37]. Another prospective study assessed the efficacy of the ketogenic diet in patients with MAE. The study included 11 patients treated with the ketogenic diet for at least 18 months. A total of six patients remained on the diet and two patients became seizure free and another two showed more than 75% seizure reduction. All of these studies showed the effectiveness of the ketogenic diet in MAE.

3. Super-refractory status epilepticus

Super-refractory status epilepticus is defined as status epilepticus that continues or recurs for 24 hours or more after the onset of anaesthetic therapy, including those cases that recur on the reduction

or withdrawal of anaesthesia[35]. Super-refractory status epilepticus is not uncommonly encountered in the neuro-intensive care unit. Retrospective studies have shown that 12 to 43% of the cases with status epilepticus became refractory[35,48,49]. In the study of Holtkamp et al.[48], 20% of the patients recurred within five days of tapering the anaesthetic agent and in all other studies, at least 50% of those requiring anaesthesia became super-refractory. It can be estimated that approximately 15% of all cases of status epilepticus admitted to the hospital will become super-refractory[35].

The use of the ketogenic diet in super-refractory status epilepticus have mostly been reported in children. The first report was conducted with six children with super-refractory status epilepticus responding to the diet. In 2010, Nabbout et al.[50] reported that nine children with super-refractory status epilepticus responded to the diet and the patients were regarded as having fever induced refractory epileptic encephalopathy in school age children. Recently, Nam et al.[36], reported the successful use of the ketogenic diet in five patients with super-refractory status epilepticus.

4. Mechanisms of ketogenic diet showing anti-epileptic activity

Ketosis has been regarded as the key feature of the ketogenic diet, and the proposed hypotheses for anti-epileptic activity of the ketogenic diet are as follows: 1) change in the nature and degree of energy metabolism in the brain, 2) change in neuronal cellular properties, and 3) change in neurotransmitter function and synaptic transmission[10]. The efficacy of the ketogenic diet develops gradually over a period of 1 to 3 weeks, suggesting that adaptive changes in gene expression are involved in its anticonvulsant effects[51,52]. In an animal study, an up-regulation of transcripts encoding energy metabolism enzymes and a 46% increase in the density of mitochondria were observed in the neuronal processes. Additionally, an increased phosphocreatine: creatine energy-store ratio was found, which indicated increased energy reserves. The hippocampal synaptic transmission in the ketogenic diet-fed animals was maintained for more than 50% longer than the controls after exposure to a metabolic stressor, suggesting that the brain tissue became more resistant to the metabolic stressor[52]. Bough[52] postulated that the observed ketogenic diet-induced production of energy metabolism compensates for the interictal metabolic deficits within epileptic foci and transient failures of gamma-aminobutyric acid-ergic inhibition.

Use of ketogenic diet in other neurologic disorders

The ketogenic diet is thought to enhance mitochondria function via many possible mechanisms. Considering the possible mitochondrial dysfunction in many neurodegenerative diseases, it can be possible to suitably adjust the ketogenic diet to the Alzheimer's disease or Parkinson disease.

1. The ketogenic diet in Alzheimer's disease

The major pathological mechanism of Alzheimer's disease is neuronal degeneration with accumulation of abnormal cellular products such as fibrillary plaques and tangles. According to a recent observation, an alteration in the function of extant neural circuits and mitochondrial homeostasis may have a pathologic role in Alzheimer's disease[9,53]. Therefore, the hypothesis that the ketogenic diet might produce beneficial effects to patients with Alzheimer's disease was introduced[54]. The results of the clinical studies have been controversial. A randomized double-blind, placebo-controlled trial of a medium chain triglyceride based ketogenic diet showed significant improvement of cognitive function in APOε4-negative patients with Alzheimer's disease. The researchers postulated that the results may be due to improved mitochondrial function, since ketone bodies have the capability to protect against the toxic effects of beta amyloid on neurons in cultured cells[55,56]. In a recent animal study, the infusion of 2-deoxy-D-glucose, a compound known to induce ketogenesis to female triple transgenic mouse model of Alzheimer's disease, resulted in a shift towards a non-amyloidogenic status and maintenance of mitochondrial bioenergetics paralleled by simultaneous reduction in oxidative stress[9,57]. There is increasing evidence that the ketogenic diet may be effective for the treatment of Alzheimer's disease through various mechanisms that reduce oxidative stress and enhance mitochondrial function[9]. The age-associated differences in the production and use of ketones and its potential side effects need to be elucidated in future studies.

2. The ketogenic diet in Parkinson's disease

The pathogenesis of Parkinson's disease involves excitotoxic degeneration of dopaminergic neurons residing in the substantia nigra, resulting in the abnormal movement, dysfunctions in cognition and other cortical functions. The impairment of mitochondrial complex I activity is hypothesized to play a role in the death of the dopaminergic neurons. It has been postulated that ketones could bypass complex I and provide an alternative fuel source. Also, enhancing mitochondrial function and increasing energy reserve might protect cells from various insults requiring high levels of energy[9,11]. There is one case series of Vanitallie et al.[58] in which the ketogenic diet was provided to seven patients with Parkinson's disease; five of them completed the study and the scores for Unified Parkinson Disease Rating Scale decreased by 43.4%. With this result, future studies on the ketogenic diet in Parkinson's disease are expected.

Conclusion

The ketogenic diet is well established as an alternative therapy for intractable epilepsy, especially in pediatric patients. Recently, there has been increasing evidence for the use in specific intractable epilepsy syndromes such as Dravet syndrome, MAE, and super-refractory status epilepticus. The diet should be considered as primary therapy in GLUT1 deficiency and PDHC deficiency because it serves as an alternative metabolic source. Also, the ketogenic diet can be considered in the treatment of other metabolic disorders, Alzheimer's disease, other neurodegenerative disorders, although more evidence is required. The use of the ketogenic diet in various conditions is mainly based on the idea that alterations in metabolism may have a neuroprotective effect or changes in neuronal excitability as well as metabolic source. However, the exact mechanisms of action await further investigations; with those, the more expanding use of ketogenic diet will be possible in the future.

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