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BRIEF COMMUNICATION

The role of ketogenic diet in the treatment of refractory status epilepticus

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Summary

Ketogenic diet (KD) is known to be effective in intractable epilepsy. However, the role of KD in refractory status epilepticus (RSE) has not been well described. The aim of this study is to explore the role of KD in patients with RSE. We retrospectively reviewed the medical records of four children and one adult with RSE between October 2006 and August 2010. All presented with status epilepticus (SE) that was presumed to be associated with viral encephalitis. After we failed to control the seizures with standard measures for SE, we tried KD. The overall seizure frequency decreased to <50% of baseline in median eight (1–19) days. At one month of KD, two patients were seizure-free, one patient showed >90% seizure reduction, and the others had >75% decrease without generalized seizures. With improvement in the RSE, we were able to taper the antiepileptic drugs (AEDs) and wean patients from prolonged mechanical ventilation. The adverse events of KD in RSE included aspiration pneumonia, gastroesophageal reflux, constipation, and hypertriglyceridemia. Those results demonstrate that KD can be a valuable therapeutic option for patients with RSE.

KEY WORDS: Ketogenic diet, Refractory status epilepticus, Viral encephalitis.

In some patients with status epilepticus (SE), the seizures may persist despite adequate treatment and progress to refractory SE (RSE). RSE is usually associated with high rates of morbidity and mortality and is regarded as a devastating medical condition (Mayer et al., 2002). The ketogenic diet (KD) has been shown to be useful in intractable epilepsy (Mady et al., 2003). Until now there have been few reports regarding the use of KD in patients with RSE (Bodenant et al., 2008; Nabbut et al., 2010; Cervenka et al., 2011). In this study, we report the successful use of the KD in patients with RSE.

Methods

Patients

Four children and one adult with RSE were treated with KD in Samsung Medical Center (Seoul, Korea) from October 2006 to August 2010.

KD protocol

We administered a commercial KD liquid composed of a 4:1 lipid to nonlipid ratio (120 kcal/100 ml, Namyang Ketonia; Namyang Dairy Products Co., Ltd, Seoul, Korea) via nasogastric tube. In two children we changed the formula to a more concentrated liquid (two-thirds of the initial volume) made by our dietician because severe gastroesophageal reflux (GER). In all patients, we escalated the amount of the KD from one third of the target amount and increased it daily, reaching the full dose in 3 days. We provided the diet four times a day while assessing gastric residue, active bowel sounds, and stool passage. We checked the blood sugar and urine ketone levels every 4–6 h until stabilization.

Clinical analysis

We investigated the clinical characteristics, laboratory results, functional status, antiepileptic drugs (AEDs), change of seizure frequency, and adverse effects after KD. This study was approved by the institutional review board of Samsung Medical Center.

Results

Clinical characteristics before KD

All patients presented with RSE, and the etiology was suspected to be viral meningoencephalitis without any

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proven viral agents in cerebrospinal fluid. All patients had nearly continuous complex partial seizures with secondary generalization at the time of KD initiation. The clinical characteristics and laboratory findings are presented in Table 1.

Initially we tried conventional management for SE with benzodiazepine, diphenylhydantoin, and phenobarbital. After those proved to be ineffective, the next step was continuous midazolam infusion (up to 1.8–3 mg/kg/h), or pentobarbital coma therapy (3–5 mg/kg/h) inducing burst-suppression patterns on continuous electroencephalography (EEG) monitoring. However, we failed to taper pentobarbital due to reappearance of nearly continuous electrical or electroclinical seizures. Despite that management, the seizures were poorly controlled and the patients were on a median of five AEDs with maximum dosages at the time of KD initiation (Table 1). In addition, four pediatric patients were under full mechanical ventilation.

Efficacy of KD

The median interval between the onset of SE and KD was one (range 0.5–14) month. The KD was maintained for a median of 5 (range 1–16) months. The median time to seizure reduction >50% was 8 days. At 1 month of KD, Patients 2 and 5 became seizure-free. In the others the generalized seizures completely disappeared, and the intensity of partial seizures was greatly reduced. There were a few breakthrough seizures in Patients 3 and 4 while decreasing AEDs, which were managed by modifying the dosage of AEDs. Patient 5 was an adult who became seizure free and fully recovered her consciousness within a week. We tapered KD at 1 month because she no longer wanted to continue the diet. Thereafter, she had some seizures, which were controlled by adding valproic acid and diphenylhydantoin. She was seizure-free for 3 months during the 6 month follow-up period. The seizure outcomes and the functional results are presented in Table 2.

Tolerability of KD

The KD was well tolerated, and the frequent adverse effects are presented in Table 2. All patients were clinically suspected to have GER, and Patient 3 was diagnosed with esophagitis by endoscopy. To prevent and mange GER, we administered domperidone, ranitidine, and lansoprazole, and placed the patients in a recumbent posture at 45 degrees during feeding. Despite that management, Patients 1 and 3

Table 1. Characteristics of patients before ketogenic diet

					Treatment before KD		
Case	Age (year)	EEG	Brain MRI	Time prior to KD (month)	AEDs	MDZ CI (duration[a])	PTB CI (duration[a])
1 (F)	14	Gen. or both F	Normal	14	PB, DPH, TPM, LEV, VGB, OXC, CLB, PGB GBP (9)	45	75
2 (M)	8	Rt. FT or Rt. O	HSI in Rt. T	4	PB, VPA, TPM, LEV, VGB, CLB (6)	6	9
3 (M)	10	Gen. or both F	HSI in Rt. T	1	PB, DPH, LZP, VPA, TPM, LEV, VGB, OXC, LTG (9)	15	11
4 (F)	4	Lt. T, Rt. TO both FCT	Leptomeningeal enhancement	1	PB, LZP, VPA, TPM, LEV, VGB (6)	5	8
5 (F)	40	Rt. or Lt. T	Nonspecific HSI in WM	0.5	DPH, VPA, TPM, LEV, CBZ (5)	0	0

KD, ketogenic diet; F, female; M, male; PB, phenobarbital; DPH, diphenylhydantoin; LZP, lorazepam; VPA, valproic acid; TPM, topiramate; LEV, levetiracetam; VGB, vigabatrin; OXC, oxcarbazepine; CLB, clobazam; GBP, gabapentin; PGB, pregabalin; MDZ, midazolam; PTB, pentobarbital; CI, continuous infusion; F, frontal; T, temporal; C, central; O, occipital; HIS, high signal intensity on T_2-weighted image; WM, white matter.
[a]Duration of therapy in days.

Table 2. Results of ketogenic diet

Case	50% reduction of Sz (day)	Sz reduction on 1 mo (%)	F/U[a] (mo)	KD[b] (mo)	Seizure outcome[c]	Functional status at last follow-up	Adverse effect of KD
1	3	75	16	16	Nondisabling partial seizures, 0–5/day	Spontaneous eye open but unable to obey, bedridden	Hypertriglyceridemia, constipation, GER
2	19	100	14	1	Nondisabling partial seizures, 0–3/month	Mild mental retardation, normal daily living	Aspiration pneumonia, constipation
3	14	75	8	8	Sz-free for 1 month	Mild mental retardation, walk alone	Constipation, severe GER
4	8	90	7	5	Sz-free for 4 months	Mental retardation walk alone	Constipation
5	7	100	6	1	Sz-free for 3 months	Normal daily living	None

Sz, seizure; mo, month; F/U, follow-up; KD, ketogenic diet; GER, gastroesophageal reflux.
[a]Duration from starting KD to last follow-up.
[b]Duration of KD.
[c]Seizure outcome at last follow-up.

had severe GER and frequent vomiting. Therefore, we tried a more concentrated formula or slow continuous feeding via a nasogastric tube over 8 h twice a day. After that, the symptoms of GER disappeared, and the KD could be continued. Patient 2 developed aspiration pneumonia after KD, so the diet was discontinued despite its efficacy for the control of RSE.

Discussion

RSE is one of the most challenging issues in epilepsy. It may last for weeks or months despite multiple AEDs and coma-inducing medications. Prolonged RSE has been reported in 20% of SE and has shown to cause high morbidity in 9–28% of patients with SE and mortality in 3–7% (Wheless, 2010).

KD is used widely to treat refractory epilepsies children. However, it has been rarely tried as an acute treatment for SE. There is a report using KD in an adult with refractory partial SE (Bodenant et al., 2008). and in two patients with prolonged nonconvulsive SE; all patients became seizure free (Wusthoff et al., 2010). Recently, there have been two reports using KD in patients with SE, who showed remarkable improvement (Nabbut et al., 2010; Cervenka et al., 2011).

When comparing those reports, our results indicate that a KD was successful even in patients with more devastating, malignant, and convulsive RSE with frequent secondary generalization. Futhermore, four patients were under full mechanical ventilator therapy. In those patients, the KD may have been life-saving treatment, because prolonged coma therapy, continuous partial seizures with frequent generalization, and use of multiple AEDs can increase the risk of fatal infection or other critical multiorgan dysfunction over time. In terms of the cognitive and functional outcomes, two patients returned to nearly normal lives, and the others obtained remarkable improvement while still showing signs of mental retardation. The cognitive outcome may be a consequence of multiple factors such as etiology or duration of SE (Holtkamp et al., 2005). It likely would be worse if the RSE were not controlled with KD.

The percentage of cases of RSE resistant to pentobarbital was reported to be 21% (Claassen et al., 2002). In this study all patients were resistant to conventional SE therapy and multiple high-dose AEDs, with four children being resistant to pentobarbital coma therapy or continuous midazolam infusion. With KD, three patients became seizure-free and the others showed remarkable improvement with tapering AEDs at last follow-up. Although those results do not verify the efficacy of KD in RSE due to the small sample size. We propose that a KD may play an important role in the treatment of RSE, especially with regard to ventilator weaning and reducing AEDs.

In patients with RSE who are on a KD, GER is an important adverse effect because of patients' low level of consciousness, immobility, hypoactive bowel movements, and prolonged ventilator therapy. In addition, high-fat diets prolong gastric emptying time, which aggravates the GER. All of these factors existed in our patients, and all patients presented with symptoms of GER to some degree. We were able to control those symptoms by feeding patients in an upright position, a more concentrated diet, a more frequent feeding schedule or continuous feeding, and by using antiemetic drugs and antacids.

The most dangerous adverse effect of KD is aspiration pneumonia associated with GER. In this study, a patient was suspected of aspiration pneumonia, and the KD was stopped. The preventive management of GER and close monitoring of symptoms will be key to successful treatment with KD for RSE.

In clinical situations, the timing of KD can be an important issue. RSE results in continuous seizures despite pentobarbital or midazolam treatment. Coma therapy usually makes the bowel hypoactive and necessitates mechanical ventilator therapy. In addition, most patients with RSE have associated viral infections and are prone to bacterial infections. In our opinion, the prerequisites for initiating KD are as follows: restoration of bowel movements, no active pulmonary infection, no suspected profound systemic infection, and no evidence of sepsis or disseminated intravascular coagulation. In addition, in the initial stages, active bowel movements can be a decisive factor for successful KD.

This study is limited by the small number of patients. Neverthless, it provides additional evidence for the beneficial role of KD in the treatment of convulsive RSE. In this study, a KD greatly reduced the frequency and intensity of seizures in RSE by 75–100%. In addition, we were able to decrease the AEDs, wean off the mechanical ventilation, and return patients to daily life after KD. Most of the patients tolerated the diet well, without any life-threatening adverse events.

Disclosure

None of the authors have any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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