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Case Report

Ketogenic diet for treatment 2-year 9 month old boy with intractable epilepsy

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Abstrak

Latar belakang : The ketogenic diet (KD) is a high-fat, low-carbohydrate, and normal-protein diet that has been used for the treatment of medically refractory childhood epilepsy since the 1920s. The KD includes 80% fat, 15% protein, and 5% carbohydrate; the ratio of fat to carbohydrate plus protein ranges from 2:1 to 4:1. The purpose of the case report was to learn benefits and factors that influence the administration of the ketogenic diet in intractable epilepsy.
Case : A 2-years 9 months old boy since 3 month of age the child begins seizure. Five month the child was diagnosed with epilepsy received one type of anti epileptic drug (AED). Seven months of age the child began control in outpatient clinic Neurology Department of Dr. Kariadi Hospital with a diagnosis of general epilepsy, were given 2 type of AEDs. Since 10 month of age the child was given 3 type of AEDs. The child still often seizure, at 15 months was diagnosed intractable epilepsy and at 29 month of age, was programed to have long term EEG and KD during hospitalization.
Conclusion : The administration of KD in 2-years 9 months old boy with intractable epilepsyshowed benefits in reducing the frequency of seizures.

Keywords : Ketogenic Diet, Intractable Epilepsy, Child

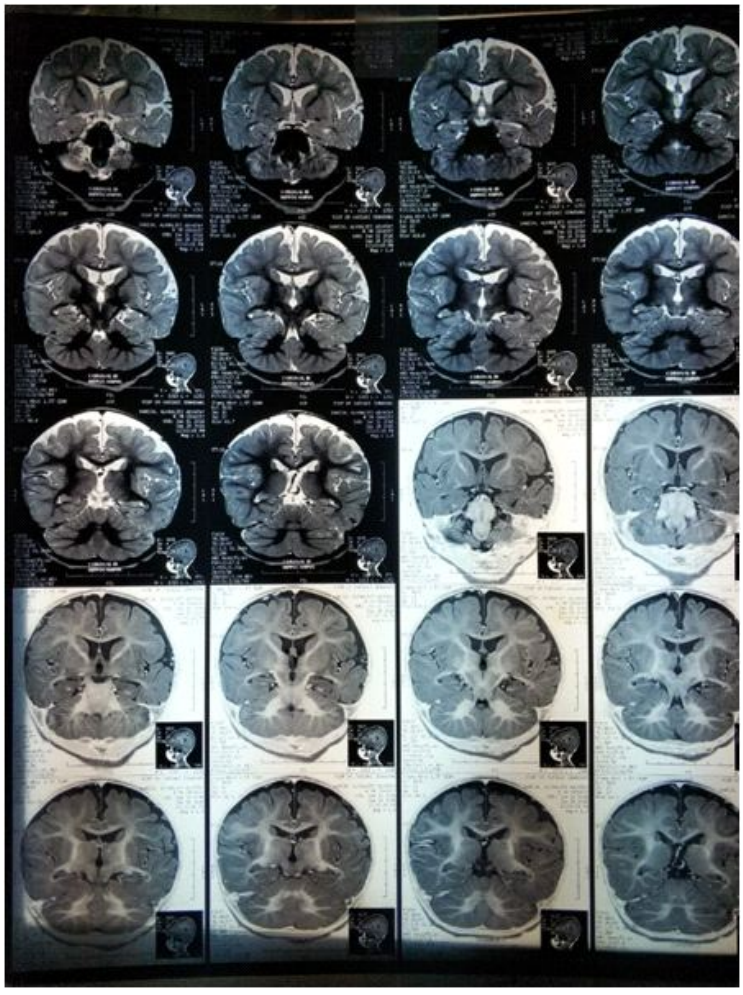
INTRODUCTION

The ketogenic diet (KD) is a high-fat, low-carbohydrate, and normal-protein diet that has been used for the treatment of medically refractory childhood epilepsy since the 1920s.The KD includes 80% fat, 15% protein, and 5% carbohydrate; the ratio of fat to carbohydrate plus protein ranges from 2:1 to 4:1, with higher ratios seen as more restrictive but more effective.[1,2] The most common ratio is 4 g of fat to 1 g of protein plus carbohydrate (described as "4:1"). This means that 90% of the energy comes from fat and 10% from protein and carbohydrate combined. Carbohydrates is depleted, while providing an alternative fuel source for the brain with another substrate (ketones), which may be anticonvulsant. Sometimes it is necessary to provide the KD at a lower ratio to increase protein or carbohydrate intake. There is some evidence that a 4:1 ratio, when used at initiation, may be more advantageous for the first 3 months.[2]

The purpose of the case report was to learn benefits and factors that influence the administration of the ketogenic diet in intractable epilepsy.

CASE PRESENTATION

A 2-years 9 months old boy since 3 months of age the child begins to seizure, seizures 3 times/day, blinking eyes and foaming mouth, stiff hands and feet, duration of seizures 10 seconds, duringseizure the child is unconscious, after the seizure the child cries, seizures are not accompanied by fever. The patient was diagnosed with epilepsy by pediatrician at Blora Hospital at 5 months of age, received anti-epilepsy drug therapy (AED), valproic acid 3ml / 12 hours, but the child was still often seizure. He routine control in Blora Hospital, patient has electro-encephalography (EEG) and ultrasonography (USG) examination of the head with the results of left hippocampus atrophy. Seizure complaints did not decrease with the treatment, the child was referred to Dr. Kariadi Hospital. Since 7 months of agethe child



Gambar 1. MRI of Head

began control in outpatient clinic Neurology Department of Dr. Kariadi Hospital with a diagnosis of general epilepsy, received valproic acid 2ml/8 hours, Keppra 250mg ½ tablet/12 hours. On October 10, the child underwent an EEG examination, with the result that no epileptic waves were found, suspected left hemisphere structure. At 10 months of age during the control, the seizure frequency was 10 times per day, the child had received valproic acid, Keppra, added therapy Topiramat 25 mg ½ tab/12 hours. Since 15 months of age children were diagnosed with intractable epilepsy. Aged 20 months the child still has still often seizures, the dose of AEDs was increased, and was programmed to undergo long term EEG examination and ketogenic diet during hospitalization.

Perinatal history the child was born from $G_1P_0A_0$ mother, 25 years of age, had no history of illness. He was born fullterm and spontaneously at midwife. Birth weight was 3000g and birth length was 48 cm. Basic immunization and booster was complete, social economic impression is poor and his father has epilepsy. Developmental historydelay in the development of the social personal sector (~20 months), gross motoric (~10 months) and language (~12 months), while the fine motor sector is age-appropriate.

On physical examination revealed body weight was 10.4 kg, height was 89 cm, bodyweight last month 11kg, head circumferrence 49cm, mid upper arm circumferrence 13.5cm, with impression of nutritional status was moderate acute malnutrition, underweight, mesocephalic. General appearance alert, heart rate of 110/minute and regular, sufficient content and tension of arterial palpation, RR 24/minute, body temperature 36.6°C. Results of cardiovascular, gastrointestinal system examinations were normal. Physiologic reflexes in upper extremities were normal, in lower were decreased, no pathologic reflexes, no clonus, tonus were decreased, muscle strenght andcranial nerves were normal.

The results of laboratory examinations on the day of admission showed Hb 9.4 g/dL, Ht 30.3%, RBC 5.11 million/mm^3, MCH 18.4 pg, MCV 59.3 fl, MCHC 31 g/dL, WBC 10.800/mm^3, platelets of 470.000/mm^3, RDW 22%, MPV 8.7 fL. Glucose level 76 mg/dL, total cholesterol 106 mg/dL, HDL 29 mg/dL, LDL 59 mg/dL,

TABEL 1
Comparison composition of the 4 Major Ketogenic Diets in Clinical Use (1000 kcal/d Provided)[6]

Diet	Fat (g)	Protein (g)	Carbohydrate (g)
Classic long-chain triglyceride			
4:1	100	17	8
3:1	96	18	14
2:1	92	20	26
1:1	77	37	40
Medium-chain triglyceride oil diet	78	25	50
Low-glycemic-index treatment	67[a]	40–60[a]	40–60
Modified Atkins diet	72[a]	68–78[a]	10–20

[a] Values are approximate

TABEL 2
Typical KD initiation regimen Johns Hopkisn Hospital Protocol[15]

Before diet	Day 1	Day 2	Day 3	Day 4
▪ Nutrition history obtained ▪ Minimize carbohydrate intake for 1 day ▪ Fasting begins after diner the evening prior to admission	▪ Admission to the hospital ▪ Conversion to carbohydrate-free medications ▪ Basic laboratory results obtained if not done previously (metabolic profile, urine calcium, urine creatine, fasting lipid profile, antiepileptic drug levels) ▪ Check fingerstick glucose every 6 hr; if <40 mg/dL, check every 2 hr ▪ If symptomatic, or glucose <25 mg/dl, give 30 ml orange juice, measure blood glucose again Parents begin classes At dinner, one third of the calculated ketogenic meal given as “eggnog” (e.g., if the full meal is calculated as 150 ml, give 50 ml at this meal) Blood glucose checks discontinued after dinner	▪ At breakfast and lunch, one-third of the calculated ketogenic meal given as “eggnog” ▪ Symptomatic ketosis (e.g., nausea, vomiting) can be relieved with small quantities of orange juice ▪ Parent classes continue ▪ At dinner, two-thirds of the calculated ketogenic meal given as “eggnog”	▪ At breakfast and lunch, two-thirds of the calculated ketogenic meal given as “eggnog” ▪ Parent classes conclude ▪ At dinner, the first full ketogenic meal is given (not “eggnog”)	▪ After breakfast (full ketogenic meal), the patient is discharged to home ▪ Prescriptions written for carbohydrate-free medications, urine ketone test strips, a sugar-free, fat-soluble multivitamin and calcium supplements, citrate salts (if indicated) ▪ Clinic follow-up appointment arranged

TABEL 3
Side effects of the KD[15]

Metabolic	GI	Cardiac	Renal	Dehydration Neurological
▪ Acidosis ▪ Weight loss ▪ Inadequate growth ▪ Rapid ketosis/acidosis ▪ Hyperlipidemia ▪ Vitamin, trace element deficiency ▪ Hyperuricemia ▪ Hematological ▪ Low Na, Mg	▪ Nausea/emesis (initiation) ▪ Constipation (classic KD) ▪ Diarrhea (MCT-KD) ▪ Worsening GERD ▪ Acute pancreatitis ▪ Hypoproteinemia	▪ Prolonged QT syndrome ▪ Cardiomyopathy	▪ Symptomatic nephrolithiasis (6%) ▪ Fanconi renal tubular acidosis	▪ Basal ganglia changes ▪ Coma, obtundation Hypoglycemia ▪ Optic neuropathy (thiamine deficiency)

Hematological	Orthopedic	Infectious Disease	Unknowns
▪ Anemia ▪ Easy bruising ▪ Leukopenia	▪ Fractures	▪ Susceptibility to infection	▪ Bone ▪ Muscle ▪ Liver

sodium 141 mmol/L, potassium 3.9 mmol/L, chlorida 102 mmol/L.

EEG long term 4–6th November 2018 showed the results did not detect interictal epilepsy, diffuse electrophysiological disorders. During epilepsy seizures that do not clearly describe the lateralization of the focus, whereas in the semilogical picture there is an impression of left mesial frontal suspicion.

MRI of Head 8th November 18 showed the left hippocampus looks slightly smaller than the right with minimal hypertensive lesions that cause part of the left hippocampus cortex blurring with a structure less image, widening the subarachnoid space of the left temporal region and the left frontal part, may be a developmental stage DD / focal atrophy cerebri.

The child were diagnosed as intractable epilepsy, moderate acute malnutrition, global developmental delayed. He was given 3 type of AEDs were Valproat acid, Topamax, and Keppra. Feeding with soft diet 2x1/2 portion, pediasure 8x100mL and were programed Ketogenic diet (KD) after completion of EEG long term.

Day 2–4 of hospitalization patient was programed for EEG longterm, patient get seizure 15–20 times/day. After completion EEG longterm, at 18.00 patient start for 24 hours fasting, measure blood glucose and keton level before begin KD. Day 5 of hospitalization (first day of KD) patient get seizure 21 times/day, KD started at 18.00, keton level was 5.2mg/dL and patient was given Ketocal 4:1 formula 5x125ml (1/3 dose of calories), blood glucose and keton were monitored every 6 hours. Day 6 of hospitalization (day 2 of KD) seizure decrease to 13 times/day, patient was given 2/3 dose of calories with formula Ketocal 4:1 8x125ml and once dinner KD 4:1. Day 7 of hospitalization (day 3 of KD) seizure 10 times/day, patient given full dose of calories with formula Ketocal 4:1 5x125ml, 3x meal KD 4:1 (@200kkal). At day 8–9 of hospitalization (day 4–5 of KD) patient vomiting once/day, and only eat half portion of meal so that the patient was given 8x125ml Ketocal through a bottle feeding. Day 10-12 days of hospitalization (day 6–8 of KD) seizure decreases from 8x/day to 5x/day and patient discharge. Seven daysafter discharge, patient control in outpatient clinic and patient only seizure once /day.

DISCUSSION

The ketogenic diet (KD) is a high-fat, low-carbohydrate, and normal-protein diet that has been used for the treatment of medically refractory childhood epilepsy since the 1920s.[3] Intractable epilepsy can be defined as as failure of ade-quate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies orin combination) to achieve sustained seizure freedom.[4] The KD includes 80% fat, 15% protein, and 5% carbohydrate; the ratio of fat to carbohydrate plus protein ranges from 2:1 to 4:1, with higher ratios seen as more restrictive but more effective. [1,2] The most common ratio is 4g of fat to 1g of protein plus carbohydrate (described as "4:1"). This means that 90% of the energy comes from fat and 10% from protein and carbohydrate combined. Carbohydrates is depleted, while providing an alternative fuel source for the brain with another substrate (ketones), which may be anticonvulsant.

Multiple variations of ketogenic diets exist, but the

most commonly prescribed are the classic ketogenic diet, the modified Atkins diet, the low-glycemic index treatment diet, the medium-chain triglyceride (MCT) diet, and the modified MCT diet.[5] The diet restricts daily calories calculated by the patient's dietitian with a distribution of 8590% long-chain fatty acid, 6 8% protein, and 24% carbohydrates.[5]

The primary indication for a KD is intractable childhood epilepsy. The treatment is typically recommended when traditional antiepileptic drugs (AEDs) have failed or AED therapy causes unacceptable side effects.

Probable benefit (at least two publications)[7]
- Glucose transporter protein 1 (GLUT-1) deficiency
- Pyruvate dehydrogenase deficiency (PDHD)
- Myoclonic-astatic epilepsy (Doose syndrome)
- Tuberous sclerosis complex
- Rett syndrome
- Severe myoclonic epilepsy of infancy (Dravet syndrome)
- Infantile spasms
- Children receiving only formula (infants or enterally fed patients)

Suggestion of Benefit (One Case Report or Series)[7]
- Selected mitochondrial disorders
- Glycogenosis type V
- Landau-Kleffner syndrome
- Lafora body disease
- Subacute sclerosing panencephalitis (SSPE)

Contraindications[7]
Absolute contraindications tothe KD include:
- pyruvate carboxylase deficiency Carnitine deficiency (primary)
- Carnitine palmitoyltransferase (CPT) I or II deficiency
- Carnitine translocase deficiency
- b–oxidation defects
- Medium–chain acyl dehydrogenase deficiency (MCAD)
- Long–chain acyl dehydrogenase deficiency (LCAD)
- Short–chain acyl dehydrogenase deficiency (SCAD)
- Long–chain 3–hydroxyacyl–CoA deficiency
- Medium–chain 3–hydroxyacyl–CoA deficiency.
- Pyruvate carboxylase deficiency
- Porphyria

Relative contraindications include :
- Inability to maintain adequate nutrition
- Surgical focus identified by neuroimaging and video EEG monitoring
- Parent or caregiver noncompliance

Most of the side effects from the ketogenic diet are related to energy and nutrient deficiencies. Lack of protein, carbohydrates, and other nutrients can result in lack of weight gain and growth inhibition, especially at a young age. Inadequate calcium intake can further impair bone mineralization in children already at risk of osteopenia due to antiseizure therapy. Lack of fibre in the diet causes constipation. Acidosis is also commonly observed. Less common are kidney stones and hyperlipidemia.[8] Adjustments to the diet (eg, increased protein and polyunsaturated fat) can be made in children with high lipid concentrations. Serious adverse events include coma and obtundation.[9] Rare side effects include cardiomyopathy, prolonged QT syndrome, vitamin and mineral deficiencies, pancreatitis, basal ganglia injury, and bruising.[10]

Monitoring

Laboratory tests for electrolytes, liver function, plasma lipid profile, proteins and complete blood count are periodically performed. Routine examinations of bone mineral density or bone enzymes are required. Typically children are kept on the diet for 1 to 2 years as long as it is beneficial and side effects are tolerable. The diet is tapered over several months by lowering the ratio of fat to protein plus carbohydrate, then slowly relaxing restrictions on weighing foods and measuring carbohydrate intake.[11] The patients compliance. Less than half of the patients remain on the diet for more than 1 year. The reasons for diet discontinuation include a lack or loss of efficacy (67%), adverse events (12%), caregivers' issues, and patients' unwillingness to continue on the diet (25%).[11] Ingestion of additional "forbidden foods" is a common cause for an insufficient level of ketosis. Attempts to prevent adverse effects from the ketogenic diet have only been met with partial success. Growth remains problematic, especially in the youngest children. Before starting the KD, the dietitian evaluates the nutritional status of the child at the initial day and evaluates growth pattern such as current height, weight and weight change. Anthropometry (weight, height, skinfold thickness) should be assessed at each visit and growth should be monitored using growth charts.

Efficacy KD in epilepsy

The ketogenic diet has been shown to be successful in controlling seizures in many observational studies.[12,13] A 2006 meta-analysis 13 of 19 observational studies (1084 patients) found that after six months of initiating a ketogenic diet, approximately 60 percent of children had a greater than 50 percent seizure reduction and 30 percent had greater than 90 percent seizure reduction.[13] The results of the meta-analysis also suggest that children maintained on a ketogenic diet may also be able to reduce their AED with better seizure control. Children that benefited the most from the diet were those with generalized seizures and those between 1 and 10 years of

age.[13] *(Level of evidence 1)*

The study in Korea showed EEGs improvement in background in 40 (72.7%) of 55 patients and a reduction in generalized and focal discharges in 41 (57.7%) of 71 and 15 (33.3%) of 45 patients.[2] *(Level of evidence 2)*

More recently, a randomized controlled trial was performed to test the efficacy of a ketogenic diet on drug-resistant childhood epilepsy.[14] *(Level of evidence 1)* The study included 145 children between 2 and 16 years of age who had at least daily seizures and had failed to respond to at least two antiepileptic drugs. Children were randomly assigned to receive a ketogenic diet immediately or to a control group, which initiated the diet 3 months after randomization. During the 3 months prior to the initiation of a ketogenic diet, the control group continued their normal diet without any dietary restrictions. The primary endpoint was a reduction in seizures at 3 months, and intention-to-treat analysis was used. At 3 months, the mean percentage of baseline seizures was significantly lower in the diet group than in the control group who had experienced an increase in seizures from baseline (62% versus 137%; $P < 0.0001$).[14] In addition, 28 children in the diet group versus 4 children in the control group experienced a greater than 50% seizure reduction ($P < 0.0001$), and five children in the diet group had greater than 90% seizure reduction compared to zero children in the control group ($P = 0.0582$).

SUMMARY

Since 3 month of age the patient begins seizure, seizures 3 times/ day, blinking eyes and foaming mouth, stiff hands and feet, duration of seizures 10 seconds, during seizure the child is unconscious, after the seizure the child cries, seizures are not accompanied by fever. 5 month of age the child was diagnosed with epilepsy received one type of AED (valproic acid), USG of head showed left hippocampus atrophy. Since 7 months of age the child began control in outpatient clinic Neurology Department of Dr. Kariadi Hospital with a diagnosis of general epilepsy were given 2 type of AEDs (valproic acid, Keppra). EEG was done at October 2016 with the result are no epileptic waves were found, suspected left hemisphere structure. Since 10 month of age (December 2016) the child were given 3 type of AEDs (valproic acid, keppra, topiramate). The patient still often seizure, 15 month of age was diagnosed intractabel epilepsy. 20 month of age the doses of AEDs were increased, the child still seizure, and at 29 month of age, was programed to have long term EEG and ketogenic diet during hospitalization.

On admission the patient was programed KD after completion EEG long term, on day 1–4 of treatment the patient seizures 15–20 times/day, 8th November KD was started with 1/3 dose with formula ketocal 4:1 3x125ml, day 2 of KD given 2/3 doses with formula ketocal 4:1 8x125ml, 1 times dinner KD. Day 3 of KD given full dose with formula Ketocal 4:1 5x125ml, 3 times meal KD @200kkal, and added therapy phenytoin, seizure was reduced into 10 times/day. Day 4–6 of KD seizure 5–8 times/day. The patient was programed to consultation neurosurgery, and the answer are focal epilepsy cannot be determined, suspicious in the left frontal, the patient needs further examination, are with intracranial EEG, and FDG PET scan. After 8 days of KD, the patient discharge from hospital. On 22th November the patient was control in outpatient clinic, at home frequency of seizure decreasing, and only seizure once/day.

The administration of KD in 2-years 9 months old boy with intractable epilepsyshowed benefits in reducing the frequency of seizures.

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