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Early- and Late-onset Complications of the Ketogenic Diet for Intractable Epilepsy

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Summary: *Purpose:* This study was undertaken to evaluate the exact limitations of the ketogenic diet (KD) and to collect data on the prevention and management of its risks.

Methods: Patients (129) who were on the KD from July 1995 to October 2001 at our epilepsy center were assessed in the study. Early-onset (within 4 weeks of the commencement of the KD until stabilization) and late-onset complications (occurring after 4 weeks) were reviewed.

Results: The most common early-onset complication was dehydration, especially in patients who started the KD with initial fasting. Gastrointestinal (GI) disturbances, such as nausea/vomiting, diarrhea, and constipation, also were frequently noted, sometimes associated with gastritis and fat intolerance. Other early-onset complications, in order of frequency, were hypertriglyceridemia, transient hyperuricemia, hypercholesterolemia, various infectious diseases, symptomatic hypoglycemia, hypoproteinemia, hypomagnesemia, repetitive hyponatremia, low concentrations of high-density lipoprotein, lipoid pneumonia due to aspiration, hepatitis, acute pancreatitis, and persistent metabolic acidosis. Late-onset complications also included osteopenia, renal stones, cardiomyopathy, secondary hypocarnitinemia, and iron-deficiency anemia. Most early- and late-onset complications were transient and successfully managed by careful follow-up and conservative strategies. However, 22 (17.1%) patients ceased the KD because of various kinds of serious complications, and four (3.1%) patients died during the KD, two of sepsis, one of cardiomyopathy, and one of lipoid pneumonia.

Conclusions: Most complications of the KD are transient and can be managed easily with various conservative treatments. However, life-threatening complications should be monitored closely during follow-up. **Key Words:** Early onset—Late onset—Complications—Ketogenic diet—Intractable epilepsy.

The ketogenic diet (KD) is accepted as a potent antiepileptic treatment for intractable childhood epilepsy (1–5) but is still used only in limited patients because of concerns for its poor tolerability and a significant number of different complications associated with it (6–10). Since the active application of KD after the mid 1990s (1–5), many kinds of complications have been reported in several studies, some of which had not been described previously (6–13).

Our study provides a detailed description of the early- and late-onset complications of the KD and data on their exact extent, severity, outcomes, and management.

METHODS

The subjects of this study were 129 patients of the Epilepsy Center at Inje University Sanggye Paik Hospital, who were treated for intractable childhood epilepsy with the KD from July 1995 to October 2001. These patients were followed up for >12 months.

Eighty-seven patients were treated with the Johns Hopkins protocol (14), starting with an initial period of fasting for ~2 days, with a fluid intake equivalent to 75% of the maintenance intake. Forty-two patients were introduced to the KD directly, with one third of the total daily calories ingested on the first day, with no initial fasting; with two thirds of the daily calories ingested on the second day; and full calories from the third day of the KD onward, as tolerated, without fluid restriction.

All patients were admitted for a mean (±SD) period of 5.4 (±0.53) days for close observation to evaluate their initial tolerance of the diet, to monitor any acute complications, and to educate their families about preparation of the diet at home. All patients received the classic KD with a lipid to nonlipid ratio of 4:1. The KD was supplemented with multivitamins, calcium at a dose of ~30 mg/kg per day, and vitamin D_2 at a dose of 40 IU/kg/day, throughout its course. L-Carnitine at a dose of 66 mg/kg/day

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also was added to the diets of 114 patients after 1998. Antiepileptic drugs (AEDs) were maintained at the same doses, although the formulas were changed to contain as little carbohydrate as possible. Acetazolamide (ACZ) was discontinued before the KD was commenced, but other AEDs, such as sodium valproic acid (VPA), topiramate (TPM), and zonisamide (ZNS), were continued during the KD.

We examined the initial tolerability of, and complications associated with, the KD, and these regularly scheduled assessments are summarized in Table 1. Criteria for the laboratory studies were those referenced in the *Nelson Textbook of Pediatrics* (15). Regular outpatient visits were recommended at monthly intervals, unless any medical illness or complication was noted. Body physics, tolerance of the KD, and clinical symptoms after its commencement were monitored closely. Patients with any abnormal finding in clinical or laboratory tests were checked more frequently during the KD.

The general efficacy of the KD was reviewed by seizure diaries, and the continuation rate of the KD in those patients with a reduction in seizures of >50% is presented as a Kaplan–Meier curve (SPSS v. 10). Early-onset complications within 4 weeks of commencement of the KD until stabilization and late-onset complications after 4 weeks of commencement were reviewed. We also compared the incidence of complications previously known to be aggravated by VPA, in patients treated with or without VPA (7,16,17). Both χ^2 analysis and unpaired *t* tests were performed with SPSS v. 10.

RESULTS

Of the 129 patients enrolled in this study, 69 were boys and 60 were girls. The mean (±SD) age of the patients at the beginning of the diet was 64.9 (±59.3) months, and the mean duration of the KD was 12.0 (±10.1) months. The classification of epilepsy and epileptic syndromes is presented in Table 2. Outcomes of the KD were as follows: 36 (27.9%) patients became seizure free; 57 (44.2%) had a decrease in seizures of >50%; and 36 (27.9%) patients had a decrease in seizures of <50% during the KD diet. However, of the 93 (72.1%) patients who were seizure free or had a reduction in seizures of >50%, 41 could not maintain the diet because of intolerance in 18 patients; various complications in 20 patients; and dropout in three patients. Fifty-two (40.3%) patients successfully maintained the KD (Fig. 1).

Within the trial period, during the first 4 weeks of the KD until stabilization, the most common complication was dehydration, defined as a reduction in body weight of >5% of the baseline value, with poor skin turgor, dried mucous membranes, and an increase in urine specific gravity of >1.020, which was noted in 60 (46.5%) patients. Fifty-two of these patients had started the KD with a period of initial fasting and constant intravenous administration of normal saline, at 75% of the maintenance level, for ~2 days (14). The second most common early-onset complication was gastrointestinal (GI) disturbances, such as nausea/vomiting, diarrhea, or constipation, which was noted in 50 (38.8%) patients. Of these GI disturbances, diarrhea was the most common complication in 42 (32.6%) patients, nausea/vomiting in 36 (27.9%), and constipation in three (2.3%). Infectious diseases, such as pneumonia, cystitis, and nonspecific febrile illnesses, were seen in 12 (9.3%) patients; lipoid pneumonia due to aspiration in three (2.3%) patients; hypercholesterolemia in 19 (14.7%) patients; hypertriglyceridemia in 35 (27.1%) patients; high-density-lipoprotein (HDL) hypocholesterolemia in five (3.9%) patients; hyperuricemia in 34 (26.4%) patients; symptomatic hypoglycemia in nine (7.0%) patients, five of whom had undergone initial fasting, and four of whom had undergone the initial step-wise caloric increase of the nonfasting protocol; hypoproteinemia in seven (5.4%) patients; hypomagnesemia in six (4.7%) patients; repetitive hyponatremia in six (4.7%) patients; hepatitis in three (2.3%) patients; and acute pancreatitis and persistent metabolic acidosis each in one patient (Table 3). Except for the patient with acute pancreatitis, most of these complications were transient and improved without any prolonged medical intervention.

After the initial 4 weeks of the KD, osteopenia occurred in 19 (14.7%) patients; renal stones in four (3.1%) patients, including one patient with hydronephrosis; iron-deficiency anemia in two (1.6%) patients; secondary

TABLE 1. *Scheduled assessments to evaluate the complications of ketogenic diet*

0, 3, 6 days and 1, 2, 3, 6, 12, 18, 24 mo
CBC with platelets, BUN/creatinine, liver profiles, electrolytes with tCO2, calcium/phosphorus/alkaline phosphatase, magnesium, uric acid, lipid profiles, blood ketone, blood sugar, urinalysis
0, 3, 6, 12, 24 mo
Blood AEDs levels, abdominal ultrasonography
0, 6, 12, 24 mo
Zinc, plain radiograph on wrist, if needed; bone densitometry, bone enzyme profiles, echocardiography

CCB, Complete blood count; BUN, blood urea nitrogen; liver profiles, total protein/albumin, total bilirubin, aspartate aminotransferase and alanine aminotransferase; lipid profiles, cholesterol, high-density lipoprotein cholesterol, triglyceride; AEDs, antiepileptic drugs; bone enzyme profiles, parathyroid hormone, 25(OH) vitamin D_3, 1.25$(OH)_2$ vitamin D_3, osteocalcin.

TABLE 2. *Patient data*

Male/Female	69:60
Age at beginning of ketogenic diet (mo)	7 mo–27 yr (mean ± SD, 64.9 ± 59.3)
Duration of ketogenic diet (mo)	1–43 (mean ± SD, 12.0 ± 10.1)
Classification; no. of patients (%)	
Lennox–Gastaut syndrome	32 (24.8)
Infantile spasms	30 (23.3)
Early infantile epileptic encephalopathy	3 (2.3)
Severe myoclonic epilepsy in infancy	12 (9.3)
Landau–Kleffner syndrome	3 (2.3)
Unclassified generalized seizure	11 (8.5)
Unclassified partial seizure	38 (29.5)

hypocarnitinemia due to the KD in two patients; and cardiomyopathy with no known cause in one patient (see Table 3). Like the early-onset complications, most late-onset complications improved with conservative management and did not require cessation of the KD.

Because the KD is an unusually high-fat diet, the lipid profiles of patients were analyzed in detail. Of the 46 patients with hypertriglyceridemia, 33 (71.7%) improved spontaneously, 12 (28.3%) persisted with modest triglyceride levels <500 mg/dl, and one patient discontinued the KD because of persistent uncontrollable hypertriglyceridemia of >1,000 mg/dl, despite a decrease in the lipid-to-nonlipid ratio to 3:1. Of the 41 patients with hypercholesterolemia, 30 (73.2%) improved spontaneously, and 11 were successfully maintained with prolonged hypercholesterolemia <500 mg/dl, sometimes with the use of cholesterol-reducing medication. Of the six patients with low concentrations of HDL cholesterol, four (66.7%) improved, whereas two (33.3%) showed persistent features with no systemic complications.

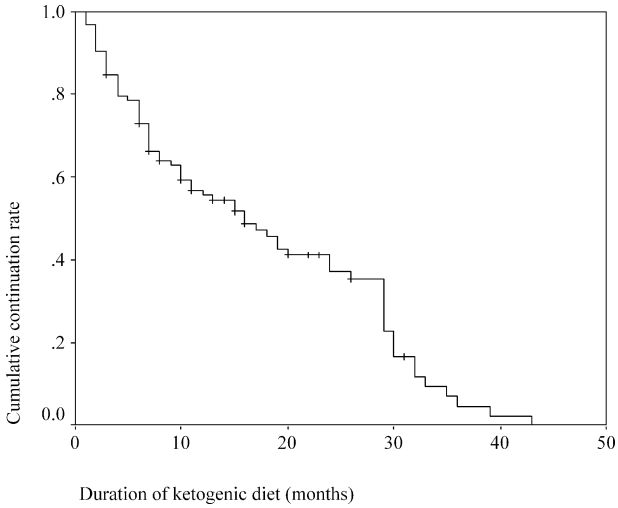

FIG. 1. Kaplan–Meier estimate of the cumulative continuation rate of the ketogenic diet (KD) in patients with a reduction in seizures of >50%. Of 93 (72.1%) patients who were seizure free or had a reduction in seizures of >50%, 41 could not maintain the diet because of intolerance in 18 patients, various complications in 20 patients, and dropout of three patients. Fifty-two (40.3%) patients successfully maintained the KD.

Sixty-seven patients stopped the KD within 6.1 (±4.7) months, and 26 of these patients, including four who died, did so because of complications. Of these 26 patients, 20 stopped despite a reduction in seizures of >50%. These 26 patients exhibited the following complications: nine (12.3%) patients were among the 73 patients with GI disturbances; five (14.7%) were among the 34 patients with infectious diseases; three (37.5%) were among the eight patients with lipoid pneumonia due to aspiration; one (5.3%) patient with persistent hypomagnesemia and tetany was among the 19 patients with hypomagnesemia; one (5.3%) had persistent metabolic acidosis; one (5.3%) had acute pancreatitis; and one (5.3%) was among the 19 patients with osteopenia. One of the 46 patients with hypertriglyceridemia discontinued the KD because of the prolonged and persistent course of this complication. Four patients died during the KD. One patient with cardiomyopathy had underlying pyruvate dehydrogenase deficiency (PDHD) and died within 12 months of the KD. One patient with lipoid pneumonia had a history of perinatal hypoxic brain insult, possibly combined with gastroesophageal reflux, and two patients with serious infectious illnesses had hypoxic brain insult due to meconium aspiration syndrome and previous encephalitis. Lipoid pneumonia and serious infectious illnesses occurred within in 2 months of the KD in these three patients. The calculated mortality rate was 8.97 per 1,000 person-years.

Of the 73 patients who continued the KD for >12 months, 47 (64.4%) showed a decrease in weight percentile, but only five (6.8%) patients were below the third percentile. Of the 14 patients who could be followed up for >6 months after discontinuation of the KD, 11 recovered their previous weight percentile.

Ninety-six patients were taking VPA during the KD, and 33 were not. The one patient with acute pancreatitis was in the group comedicated with VPA. The one patient with cardiomyopathy and the patient with secondary hypocarnitinemia were among the VPA-nonmedicated group. Hepatitis occurred in eight (9.1%) of the 96 patients in the comedicated group and in two (6.5%) of the 33 patients in the nonmedicated group ($p = 0.67$). No statistically significant difference was found between the two groups in the incidence of any kind of complication. Strong ketosis developed within 2.5 ± 0.7 days in the VPA comedicated group, compared with 2.3 ± 0.5 days in the nonmedicated group; these values are not significantly different ($p = 0.13$).

DISCUSSION

Dehydration was the most common early-onset complication, especially during the initial fasting period of the

TABLE 3. *Early- and late-onset complications of the ketogenic diet*

	No. of patients (%)		
	Early onset	Late onset	Early and late onset
Dehydration[a]	60 (46.5)		
Gastrointestinal discomfort[b]	50 (38.7)	36 (27.9)	13 (10.1)
Infectious disease[c]	12 (9.3)	27 (20.9)	5 (3.9)
Lipoid aspiration pneumonia	3 (2.3)	6 (4.7)	1 (0.8)
Lipid profiles			
Hypertriglyceridemia	35 (27.1)	26 (20.2)	15 (11.6)
Hypercholesterolemia	19 (14.7)	25 (19.4)	3 (2.3)
Hypo HDL[d] cholesterolemia	5 (3.9)	1 (0.8)	
Hyperuricemia	34 (26.4)	10 (7.8)	
Symptomatic hypoglycemia[e]	9 (7.0)	1 (0.8)	1 (0.8%)
Hypoproteinemia	7 (5.5)	5 (3.9)	
Hypomagnesemia	6 (4.7)	14 (10.9)	1 (0.8)
Repeated hyponatremia	6 (4.7)		
Hepatitis	3 (2.3)	7 (5.4)	
Acute pancreatitis	1 (0.8)		
Persistent metabolic acidosis	1 (0.8)		
Osteopenia		19 (14.7)	
Renal stone		4 (3.1)	
Hydronephrosis		1 (0.8)	
Iron-deficiency anemia		2 (1.6)	
Secondary hypocarnitinemia		2 (1.6)	
Cardiomyopathy		1 (0.8)	

[a] A body weight reduction of >5% of the baseline and marked dried skin or mucous turgor with the increased urine specific gravity of >1.020.
[b] Nausea/vomiting, diarrhea, constipation.
[c] Pneumonia, cystitis, nonspecific febrile illness.
[d] High-density lipoprotein.
[e] <40 mg/dl of blood sugar, with nausea, lethargy, perspiration, dizziness, tachycardia, and pale appearance.

classic KD protocol, despite constant intravenous administration of normal saline at 75% of the maintenance level. By modifying the protocol to omit the initial period of fasting, we could prevent acute dehydration in most patients, with no difference in the time to ketosis or in the efficacy of the diet (18). Wirrell et al. (19) also reported similar results with a nonfasting protocol. Initial fasting was previously considered important to screen for underlying metabolic diseases, which can be exacerbated devastatingly by the KD (6,20,21). However, most of these rare disorders, such as fatty acid oxidation defect, pyruvate carboxylase deficiency, and cytochrome oxidase deficiency, usually occur in combination with other major neurologic features, other than epilepsy, and can therefore be diagnosed with careful clinical and laboratory assessments before the commencement of the KD (22). Severe, prolonged symptomatic hypoglycemia can complicate underlying metabolic diseases with devastating results, and these diseases should be screened for before the KD is commenced (20). Transient hypoglycemia is often a complication of the KD, usually in the initial period of fasting but also during the initial step-wise increase in caloric intake in the nonfasting protocol. However, most patients experiencing this recovered without assistance and showed no hypoglycemic symptoms. Nine patients with symptomatic hypoglycemia also had only transient hypoglycemia, which was successfully treated with a small drink of orange juice. These patients had shown no evidence of underlying metabolic disease in the previous metabolic screening.

The next most common early- and late-onset complication was GI disturbance, involving nausea/vomiting, diarrhea, or constipation. GI disturbance is a very important complication and is directly related to poor tolerance of the diet, entailing significant resistance to the KD and even affecting its efficacy. The symptoms of GI disturbance were seen in 73 (56.6%) patients. Diarrhea was the most common of these symptoms, but most cases were transient and easily controlled, sometimes by short-term antidiarrhea medication. Defective absorption and intolerance of fat may cause this transient diarrhea, and a period should be allowed for the GI system to adapt to the high-lipid diet. A high incidence of cricopharyngeal incoordination and gastroesophageal reflux is found among children with intractable epilepsy (23). A high-fat diet prolongs the gastric emptying time and causes vomiting, especially in patients with gastroesophageal reflux (24). In this study, one handicapped patient who possibly had gastroesophageal reflux died of lipoid pneumonia. Gastritis is a complication in many patients with intractable epilepsy who have undergone prolonged treatment with multiple AEDs, especially steroids (25), which might be a factor contributing to vomiting. Moreover, psychological resistance to the sudden change from previously

familiar food to a new and unpalatable diet might be one of the main causes of nausea and vomiting. All these factors can contribute to nausea and vomiting, but most of these symptoms could be controlled by modification of the diet menu, frequent intake of small amounts, intermittent use of GI medications such as antiemetics, GI tract regulators, and antacids that address the underlying causes. In the five patients with severe gastroesophageal reflux, fundoplication could be helpful in the prevention of lipoid pneumonia from aspiration. Psychological resistance can be managed with a strict and positive attitude to the diet among parents and careful modification of the menu by a dietitian. Constipation might be caused by a decreased intake of fiber, a decreased volume of food, or the poor mobilization usually seen in handicapped children (24). Constipation was successfully controlled in most patients with oral laxatives and intermittent enemas.

Acute pancreatitis is a rare but serious complication that is often fatal (12). Pancreatitis can be caused by hypertriglyceridemia (26) and sometimes by the concomitant use of AEDs, especially VPA (27). Discontinuation of the KD and adequate supportive treatment are required for successful recovery. Our one patient who had pancreatitis early in the KD had been treated with VPA for 2 years before undertaking the diet and recovered from pancreatitis only after abandoning the KD. Infectious diseases were a relatively common complication in the early and late stages of the KD. No definite immunologic impairment related to the KD has been reported, except an impaired neutrophil function observed in vitro (28). However, it is possible that an unbalanced diet, with protein restricted to the minimal requirement, might cause immunologic dysfunction. We observed fulminating sepsis in seven patients, who required intensive care, with symptoms of high fever, unstable vital signs, and/or were positive for cultured organisms in the blood, cerebrospinal fluid, or urine. These patients were discontinued from the KD. Two of these patients died, even with active antibiotic intervention and conservative management. Of the seven patients with sepsis, four patients had suggestive mitochondrial cytopathy with increased lactate, pyruvate, and Kreb's cycle intermediates identified by analysis of urine organic acids, although these results were not confirmed by further studies, such as muscle biopsy or enzyme analysis. All of the four were severely retarded, with severe mental and motor developmental handicaps, as well as having prolonged intractable epilepsy with Lennox–Gastaut syndrome. These patients recovered from the fulminating infection after potent antibiotic therapy and supportive care after discontinuation of the KD. Two other patients had histories of hypoxic insult from perinatal asphyxia and had severe mental and motor developmental retardation and intractable epilepsy with infantile spasms. One patient, who died of pneumonia and sepsis, had a history of meconium aspiration syndrome and pneumothorax in the perinatal period. The seventh patient, who died of pneumonia and acute respiratory distress syndrome, had a history of previous encephalitis and a severe degree of destructive encephalopathy, with serious developmental retardation and infantile spasms. No evidence was found of underlying immunologic problems in all patients, on the basis of screening with laboratory tests. Most other infectious illnesses were well controlled with the appropriate antibiotics, without discontinuation of the KD.

Lipid profiles can be altered by prolonged ingestion of high-lipid diets. However, Swink et al. (29) suggested that the atheroma produced by the KD can be absorbed after return to a normal diet. Livingston et al. (30) reported that the KD did not influence blood pressure or increase the risk of cardiovascular complications in long-term follow-up studies. Wheless and Ashwal (24) noted that the diet may be continued unless cholesterol levels increase to >1,000 mg/dl and remain there. In our patients, hypercholesterolemia was noted in 41 patients, and hypertriglyceridemia in 46 patients. As we reported in detail (31), most improved spontaneously or maintained a level <500 mg/dl by decreasing the lipid-to-nonlipid ratio to 3:1 or with the use of cholesterol-reducing medication. Only one patient with prolonged, persistent hypertriglyceridemia of >1,000 mg/dl stopped the KD. Because the long-term complications from lipemic conditions are unknown, further long-term follow-up studies are required.

De Vivo and DiMauro (22) suggested that hepatitis could be caused by impairment of fatty acid oxidation or carnitine deficiency, especially in patients also receiving treatment with VPA. Although L-carnitine was routinely prescribed for our patients, hepatitis occurred in eight of the 88 patients comedicated with VPA and in two of the 31 patients not receiving VPA. We found no statistically significant correlation between hepatitis and the use of VPA. All patients with hepatitis showed aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of <200 mg/dl and persisted with the KD.

Various complications related to biochemical abnormalities, such as hyperuricemia, hyponatremia, persistent acidosis, hypomagnesemia, and hypoproteinemia, were observed. Hyperuricemia can be caused by protracted seizures, dehydration, and acidosis (9) and can be managed with conservative treatment. The repetitive hyponatremia of six patients was related to dehydration. One patient with persistent hypomagnesemia with tetany and another patient with persistent metabolic acidosis had to discontinue the KD. The cause of this persistent metabolic acidosis was not discovered, despite extensive metabolic analysis. The mechanism underlying hypoproteinemia was not identified, although gluconeogenic consumption due to carbohydrate restriction was suspected (7). Patients with hypoproteinemia improved only after an increase in protein intake from 1 g/kg/day to 1.5 g/kg/day while the lipid-to-nonlipid ratio was maintained.

Complications occurring in the late period of the KD were osteopenia, renal stones, and cardiac problems. Hahn et al. (32) suggested that KD patients may have complications involving the biochemical abnormalities of vitamin D-deficiency–induced osteopenia. This nutritional defect, together with calcium loss from immobilization, is suspected to contribute to bone demineralization. In all the patients in this study, laboratory evaluation of osteopenia was followed by routine supplementation with calcium and vitamin D to prevent this complication. However, osteopenia occurred in 19 patients, one of whom had a pathological fracture and ceased the KD. Before osteopenia was diagnosed, the mean (±SD) duration of the KD was 12.3 (±6.5) months. Among 19 patients with osteopenia, three patients were not able to walk, including one patient with cerebral palsy who was not bedridden. The other 16 patients also showed somewhat delayed motor development. Although most patients with intractable epilepsy in this study showed delayed motor development, this was not a characteristic finding among patients with osteopenia. The causes of osteopenia were intolerance to the KD (malnutrition) and lack of exposure to sunlight, rather than immobilization. For patients diagnosed with osteopenia, usually by plain radiograph of the wrist, we recommended weight-bearing exercise and exposure to sunlight. Bone densitometry and bone enzyme profiles also were examined at follow-up, the results of which were consulted when deciding the dose of calcium or vitamin D supplements. Bone densitometry is a sensitive method with which to evaluate osteopenia, but, unfortunately, referential age-related data are not yet available in our region, so we compared the results of bone densitometry serially through the follow-up data.

Prophylactic supplementation with calcium and vitamin D sometimes fails to prevent the progress of osteoporotic changes, but further supplementation with both might improve this condition in all severely osteopenic patients. If osteopenia is suspected because of plain radiograph or laboratory results, serial follow-up with bone densitometry, bone hormone studies, and carefully monitored additional doses of calcium and vitamin D are required to prevent the progress of osteopenia during the KD.

Urolithiasis is another possible complication of the KD (9,10). The stones have been reported to be uric acid, calcium oxalate, or a mixture of calcium oxalate and calcium phosphate/uric acid (9,10). All four patients in our study had calcium oxalate stones. Chronic acidosis, dehydration, and fat malabsorption are responsible for the formation of calcium oxalate stones (9). Because evidence exists that increased fluid intake does not diminish the efficacy of the KD in controlling seizures and blood ketone levels, hydration with larger amounts of water should be encouraged to prevent the formation of renal stones (9). Carbonic anhydrase inhibitors, such as TPM and ZNS, also can aggravate the formation of renal stones, and Kossoff et al. (33) advocated discontinuation of any carbonic anhydrase inhibitor if renal stones were found. The four patients in this study with calcium oxalate stones had been receiving TPM. Three of these patients could continue the KD and improved with conservative management such as the discontinuation of TPM, an increase in fluid intake, and hydrochlorothiazide (2 mg/kg/day), and one patient was successfully treated with extracorporeal shock-wave lithotripsy (ESWL). The mean latency period from initiation of the KD to symptomatic renal lithiasis has been reported to be 18 months (range, 14–24 months) (10) or between 7 and 22 months (9), but in this study, the mean latency period was 8.5 months (range, 5–14 months). Repeated urinary studies with ultrasonography are important to detect and prevent this complication.

Cardiomyopathy is a rare but serious complication, often proving to be fatal (11). Bradycardia, diminished QRS voltage, and prolonged QT intervals have been reported to correlate significantly with selenium deficiency, low serum bicarbonate levels, high β-hydroxybutyrate levels, and carnitine deficiency. If these conditions are monitored carefully, the KD can be continued with periodic echocardiographic follow-ups, unless systolic dysfunction is found (11,17,34). In this study, one patient died of cardiomyopathy during the 12 months of the KD, despite initially normal cardiac function and periodic echocardiography. The patient showed no evidence of carnitine deficiency but was PDHD, confirmed by enzyme assay with cultured fibroblasts. The KD is known to be effective for pyruvate dehydrogenase E_1 deficiency (35), but Weber et al. (36) stated the caveats when considering the KD for the treatment of PHDH. In this patient, prolonged poor intake of the diet, resulting from food refusal, may have caused energy failure, and a deficiency of minor elements, such as selenium, may have been responsible for her cardiomyopathy, although selenium levels were not checked. The direct cause of death in this patient was respiratory failure from pneumonia and acute respiratory distress syndrome complicated by cardiomyopathy. The relation between KD, PDHD, cardiomyopathy, and fatal outcome remains to be considered. Autopsy was not preformed on this patient because of refusal by her parents.

Two patients had secondary hypocarnitinemia before routine supplementation with L-carnitine. Hypocarnitinemia can be caused by a decreased intake of carnitine during the KD, an increase in demand, secondarily from the long-term use of AEDs, especially VPA and phenobarbital (PB), or rarely as the result of underlying primary hypocarnitinemia (17). Both hypocarnitinemic patients in this study manifested generalized weakness and mild cardiomegaly, and one experienced excessive fatigue and decreased muscle power. Neither patient had underlying primary hypocarnitinemia, and both were improved with L-carnitine replacement alone, with continuation of

the KD. After routine supplementation with L-carnitine at 66 mg/kg/day, no other patients had hypocarnitinemia. Rutledge (37) reported that the ketogenic diet may induce carnitine deficiency, which in turn may interfere with the seizure-reducing effects of the diet. However, because the risk of carnitine deficiency outweighs the seizure-reducing effects and because it is not easy to recognize the carinitine-deficient state, we recommend routine supplementation.

In addition to these complications, lipemia retinalis, bilateral optic neuropathy, alopecia, renal tubular acidosis, and hemolytic anemia have been reported rarely (7,38). Our patients were routinely supplemented with vitamin B, and optic problems, which are rarely reported with vitamin B supplementation, were not observed (39).

VPA has been shown experimentally to reduce fasting ketonemia, but clinically, VPA therapy has not precluded initiation of the KD or the achievement of adequate ketosis (40,41). In our experience, VPA did not affect the achievement of adequate ketosis and was not related to, or did not increase the occurrence of, any complication, including acute pancreatitis, cardiomyopathy, or secondary hypocarnitinemia.

In conclusion, KD can cause various complications, but most of these can be improved with conservative management, with no need to stop the KD. However, we sometimes experienced serious complications requiring interruption of the KD, and life-threatening infectious diseases, lipoid pneumonia due to aspiration, and cardiomyopathy produced fatal outcomes. The mortality rate was not greater than that associated with the natural progression of symptomatic childhood epilepsy (42). However, to prevent fatal outcomes with the KD, early detection of serious illness and active intervention seem to be most important, as is adequate nutritional support and extensive screening for underlying metabolic or immunologic disorders.

REFERENCES

1. Nordli DR Jr, DeVivo DC. The ketogenic diet revisited: back to the future. *Epilepsia* 1997;38:743–9.
2. Vining EPG, Freeman JM, Ballaban-Gil K, et al. A multicenter study of the efficacy of the ketogenic diet. *Arch Neurol* 1998;55:1433–7.
3. Freeman JM, Vining EPG, Pillas DJ, et al. The efficacy of the ketogenic diet, 1998: a prospective evaluation of intervention in 150 children. *Pediatrics* 1998;102:1358–63.
4. Katyal NG, Koehler AN, McGhee B, et al. The ketogenic diet in refractory epilepsy: the experience of the Children's Hospital of Pittsburgh. *Clin Pediatr* 2000;39:153–9.
5. Hemingway C, Freeman JM, Pillas DJ, et al. The ketogenic diet: a 3- to 6-year follow-up of 150 children enrolled prospectively. *Pediatrics* 2001;108:898–905.
6. DeVivo DC, Haymond MW, Lechkie MP, et al. The clinical and biochemical implications of pyruvate carboxylase deficiency. *J Clin Endocrinol Metab* 1977;45:1281–96.
7. Ballaban-Gil K, Callahan C, O'Dell C, et al. Complications of the ketogenic diet. *Epilepsia* 1998;39:744–8.
8. Chesney D, Brouhard BH, Wyllie E, et al. Biochemical abnormalities of the ketogenic diet in children. *Clin Pediatr* 1999;38:107–9.
9. Furth SL, Casy JC, Pyzik PL, et al. Risk factors for urolithiasis in children on the ketogenic diet. *Pediatr Nephrol* 2000;15:125–8.
10. Kielb S, Koo HP, Bloom DA, et al. Nephrolithiasis associated with the ketogenic diet. *J Urol* 2000;164:464–6.
11. Best TH, Franz DN, Gilbert DL, et al. Cardiac complications in pediatric patients on the ketogenic diet. *Neurology* 2000;54:2328–30.
12. Stewart WA, Gordon K, Camfield P. Acute pancreatitis causing death in a child on the ketogenic diet. *J Child Neurol* 2001;16:633–5.
13. Berry-Kravis E, Booth G, Taylor A, et al. Bruising and the ketogenic diet: evidence for diet-induced changes in platelet function. *Ann Neurol* 2001;49:98–103.
14. Freeman JM, Kelly MT, Freeman JB. *The Epilepsy Diet Treatment: An Introduction to the Ketogenic Diet*. New York: Demos, 1994:65–100.
15. Nicholson JF, Pesce MA. Reference ranges for laboratory tests and procedures. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson textbook of pediatrics*. 16th ed. Philadelphia: WB Saunders, 2000:2181–224.
16. Prasad AN, Stafstrom CE, Holmes GL. Alternative epilepsy therapies: the ketogenic diet, immunoglobulins, and steroids. *Epilepsia* 1996:37(suppl 1):81–95.
17. De Vivo DC, Bohan TP, Coulter DL, et al. L-carnitine supplementation in childhood epilepsy: current perspectives. *Epilepsia* 1998:1216–25.
18. Park JC, Kim HD. Benefits of nonfasting ketogenic diet in intractable childhood epilepsy as compared with initial fasting ketogenic diet. *Epilepsia* 2001;42(suppl 7):214–5.
19. Wirrell EC, Darwish HZ, Williams-Dyjur C, et al. Is a fast necessary when initiating the ketogenic diet? *J Child Neurol* 2002;17:179–82.
20. Nordli DR Jr, DeVivo DC. The ketogenic diet. In: Wyllie E, ed. *The treatment of epilepsy, principles and practice*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001:1001–6.
21. Demeritte EL, Ventimiglia J, Coyne M, et al. Organic acid disorders and the ketogenic diet. *Ann Neurol* 1996;40:305.
22. DeVivo DC, DiMauro S. Mitochondrial diseases. In: Swaiman KF, Ashwal S, eds. *Pediatric neurology, principles and practice*. 3rd ed. St. Louis: Mosby, 1999:494–509.
23. Chong SK. Gastrointestinal problems in the handicapped child. *Curr Opin Pediatr* 2001;13:441–6.
24. Wheless JW, Ashwal S. The ketogenic diet. In: Swaiman KF, ed. *Pediatric neurology: principles and practice*. 3rd ed. St. Louis: Mosby, 1999:719–28.
25. Hrachovy RA. ACTH and steroid. In: Engel J Jr, Pedley TA, eds. *Epilepsy, a comprehensive textbook*. Philadelphia: Lippincott-Raven, 1998:1463–73.
26. Toskes PP. Hyperlipidemic pancreatitis. *Gastroenterol Clin North Am* 1990;19:783–91.
27. Chapman SA, Wacksman GP, Patterson BD. Pancreatitis associated with valproic acid: a review of the literature. *Pharmacotherapy* 2001;21:1549–60.
28. Woody RC, Steele RW, Knapple W, et al. Impaired neutrophil function in children with seizures treated with the ketogenic diet. *J Pediatr* 1989;115:427–30.
29. Swink TD, Vining EPG, Freeman JM. The ketogenic diet: 1997. *Adv Pediatr* 1997;44:297–329.
30. Livingstone S, Pauli LL, Pruce I. Ketogenic diet in the treatment of childhood epilepsy. *Dev Med Child Neurol* 1977;19:833–4.
31. Park JC, Park MJ, Kim HD. Lipid profiles in patient with ketogenic diet for intractable childhood epilepsy. *J Korean Epilepsy Soc* 2002;6:124–7.
32. Hahn TJ, Halstead LR, De Vivo DC. Disordered mineral metabolism produced by ketogenic diet therapy. *Calcif Tissue Int* 1979;28:17–22.
33. Kossoff EH, Pyzik PL, Furth SL, et al. Kidney stones, carbonic anhydrase inhibitors, and the ketogenic diet. *Epilepsia* 2002;43:1168–71.
34. Chee CM, Lutchka L. Ketogenic diet: unrecognized selenium deficiency. *Epilpesia* 1998;39(suppl 6):228.
35. Wexler ID, Hemalatha SG, McConnell J, et al. Outcome of pyruvate dehydrogenase deficiency treated with ketogenic diets:

studies in patients with identical mutations. *Neurology* 1997;49:1655–61.
36. Weber TA, Antognetti MR, Stacpoole PW. Caveats when considering ketogenic diets for the treatment of pyruvate dehydrogenase complex deficiency. *J Pediatr* 2001;138:390–5.
37. Rutledge SL, Geraghry MT, Vining EPG, et al. Hypocarnitemia and the ketogenic diet. *Ann Neurol* 1989;26:472.
38. Livinston S. *Comprehensive management of epilepsy in infancy, childhood and adolescence*. Springfield, IL: Charles C Thomas, 1972.
39. Hoyt CS, Billson FA. Optic neuropathy in ketogenic diet. *Br J Ophthalmol* 1979;63:191.
40. Thurston JH, Carroll JE, Dodson WE, et al. Chronic valproate administration reduces fasting ketonemia in children. *Neurology* 1983;33:1348.
41. Turnbull DM, Dick DJ, Wilson L, et al. Valproate causes metabolic disturbance in normal man. *J Neurol Neurosurg Psychiatry* 1986;49:405.
42. Sillanpää M, Jalava M, Laleva O, et al. Long-term prognosis of seizures with onset in childhood. *N Engl J Med* 1998;338:1715–22.