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ARTICLE

Long-Term Outcome of the Ketogenic Diet for Intractable Childhood Epilepsy With Focal Malformation of Cortical Development

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What's Known on This Subject

For pediatric candidates for epilepsy surgery, MCD is the predominant etiology. Nevertheless, epilepsy surgery is still challenging because of seizure relapse and morbidity. The KD has been used as a safe and effective alternative therapy for intractable childhood epilepsy.

What This Study Adds

Most series published have included only a small number of patients with focal MCD. This study evaluates the efficacy of the KD and the long-term prognoses after its successful completion in patients with intractable childhood epilepsy from focal MCD.

ABSTRACT

OBJECTIVE. We evaluated the efficacy and long-term outcome of the ketogenic diet in patients with intractable childhood epilepsy as a result of focal malformation of cortical development.

METHODS. A retrospective analysis evaluated seizure outcomes of 47 patients who had intractable epilepsy from (and) surgically remediable focal malformation of cortical development and were first treated with the classic ketogenic diet, involving the 4:1 lipid/nonlipid ratio. The long-term prognosis of 21 patients, who became seizure-free 3 months after the ketogenic diet, was followed up with that of 22 patients who eventually underwent epilepsy surgery.

RESULTS. Three months after diet initiation, 29 (61.7%) patients showed a reduction in seizure frequency of >50%, including 21 (44.7%) who became seizure-free. Of the 21 patients with complete seizure control at 3 months, 16 (76.2%) successfully completed the diet for 2 years without relapse, and 10 (47.6%) have remained seizure-free after cessation of the diet (mean follow-up for 3 years and 10 months), including 1 patient who remained seizure-free with additional medication after a relapse. Of the 22 patients who underwent epilepsy surgery, a seizure-free outcome was obtained for 13 (59.1%).

CONCLUSIONS. The ketogenic diet should be considered to be an additional option even in patients with focal malformation of cortical development, and long-term seizure-free outcome can be expected for patients who become seizure-free 3 months after the diet. *Pediatrics* 2008;122:e330–e333

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Key Words
ketogenic diet, epilepsy surgery, childhood epilepsy, malformation of cortical development

Abbreviations
MCD—malformation of cortical development
AED—antiepileptic drug
KD— ketogenic diet
TR—repetition time
TE— echo time

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THE CAUSES OF intractable childhood epilepsy are quite variable, and modern imaging techniques have improved the detection of malformation of cortical development (MCD), which frequently evolves to secondary generalized epileptic encephalopathy.[1–3] In pediatric candidates for epilepsy surgery, focal MCD is the predominant etiology.[4] Surgical treatment of highly selected patients with a well-demarcated epileptic focus can provide complete seizure control and dramatic catch-up in developmental progress, without serious complications.[5,6] Nevertheless, despite such gratifying results from epilepsy surgery, surgical intervention in most patients is still challenging because of the potential risks of seizure relapse and functional morbidity.[7]

Since the resurgence of the ketogenic diet (KD) (a high-fat, adequate-protein, low-carbohydrate diet) in the mid-1990s, it has been used extensively and recognized as a safe and effective alternative therapy for intractable childhood epilepsy.[8] Patients with MCD, who have a more immature cerebral cortex, may respond particularly well to the diet.[9] Most series published to date, however, have included only a small number of patients with focal MCD and were limited by an absence of data describing the long-term prognosis after completion of the diet therapy.[10,11] We aimed to evaluate the efficacy of the KD and the long-term prognosis after its successful completion and to determine the role of the diet in patients with intractable childhood epilepsy from focal MCD.

METHODS

The patients in this study were 47 patients who were treated for epilepsy at the 2 epilepsy centers at Yonsei University and Inje University (Seoul, Korea). These were patients who had been experiencing >4 seizures per month, with seizures uncontrolled by ≥3 antiepileptic drugs. In all patients, focal MCD related to the intractable seizures had been discovered by high-resolution MRI, and in 22 patients, the diagnosis was later confirmed by histopathologic examinations after epilepsy surgery. MRI scans were obtained with a 1.5-T magnetic resonance system (Marconi, Cleveland, OH), using spin-echo T1-weighted images (T1WI, repetition time [TR]/echo time [TE] 476/16 milliseconds) and fast spin-echo T2-weighted images (T2WI, TR/TE 4000/105 milliseconds). Additional high-resolution MRIs using three-dimensional RF spoiled Fourier acquired steady state with thin (1.6- to 2.0-mm) thickness (TR/TE 30/4.47 milliseconds, flip angle 30°), and fast inversion recovery for myelin suppression with thin thickness (TR/TE/inversion time 6500/54/200 milliseconds) were also obtained. MCD findings were confirmed by 2 independent neuroradiologists who were blinded to the clinical and electroencephalogram information. Histopathologic examinations followed the Palmini and Luders classification[12]: type 1 (A = isolated architectural abnormalities, B = plus giant or immature but not dysmorphic neurons), and type 2 (A = architectural abnormalities with dysmorphic neurons but without balloon cells, B = with balloon cells). In addition, mild cortical dysplasia was defined as ectopically placed neurons in or adjacent to the first cortical layer or microscopic neuronal heterotopia outside the layer.

Surgical treatment had been considered for the patients, but the caregivers/parents agreed to prioritize the trial of the KD. All patients received the classic KD as an add-on treatment with a lipid/nonlipid ratio of 4:1 without initial fasting and fluid restriction. We previously published a detailed protocol for the classic KD, scheduled assessments for evaluating complications, and used the method to obtain data, as described in previous reports.[13,14] We observed initial outcomes after 3 months on the KD and decided whether the diet should be continued. The KD was maintained for 2 years and subsequently discontinued with a gradual decrease in the ratio for 4 to 6 months. The patients whose seizures were not completely controlled during the KD or who had recurrences after discontinuing the KD underwent evaluation for surgical treatment. All patients were followed for at least 12 months after discontinuation or completion of the KD.

RESULTS

Patient Characteristics

Of the 47 patients (29 male, 18 female), 15 (31.9%) had a diagnosis of infantile spasms, 17 (36.2%) of Lennox-Gastaut syndrome, and 15 (31.9%) of partial seizures. Patients experienced their first seizure at a mean ± SD age of 18.6 ± 28.7 months. The mean ± SD age of the patients at the beginning of the diet was 47.2 ± 33.7 months. The mean ± SD duration of the patients' epilepsy before the KD was 28.6 ± 24.2 months.

TABLE 1 **Clinical Profiles of Patients With Intractable Childhood Epilepsy and Focal MCD (*N* = 47)**

Parameter	Value
Male/female, *n*/*n*	29/18
Age on seizure onset, mean ± SD, mo	18.6 ± 28.7
Age on beginning the KD, mean ± SD, mo	47.2 ± 33.7
Duration from seizure onset to the KD, mean ± SD, mo	28.6 ± 24.2
Epilepsy classification, *n* (%)	
Infantile spasms	15 (31.9)
Lennox-Gastaut syndrome	17 (36.2)
Partial epilepsy	15 (31.9)
Localizations of MCD, *n* (%)	
Frontal	25 (53.2)
Temporal	5 (10.6)
Parieto-occipital	8 (17.1)
Multilobar	9 (19.1)
MRI findings, *n* (%)	
Focal cortical dysplasia[a]	42 (89.4)
Focal nodular heterotopia	1 (2.1)
Schizencephaly	1 (2.1)
Pachygyria	1 (2.1)
Hemimegalencephaly	2 (4.3)

[a] MRI findings of focal cortical dysplasia, consisting of focal cortical thickening with or without blurring at the gray–white matter junction/focal T2 prolongation of subcortical white matter.

MRI findings included focal cortical thickening, blurring at the gray–white matter junction, dysgyria, and focal T_2-prolongation of subcortical white matter in 42 patients; focal nodular heterotopia (1 patient); schizencephaly (1 patient); and pachygyria (1 patient). Two patients had hemimegalencephaly. Localization of the MCD was in the frontal lobe in 25 (53.2%) patients, the parieto-occipital lobes in 8 (17.1%), the temporal lobe in 5 (10.6%), and multilobar areas (involving >1 lobe in a single hemisphere) in 9 (19.1%) patients. The detailed clinical profiles and MRI findings are summarized in Table 1.

Efficacy and Long-Term Outcomes of the KD

Three months after initiating the diet, 29 (61.7%) patients remained on the diet and showed a >50% reduction in seizure frequency, including 21 (44.7%) who became seizure-free. Among the 21 patients with seizure-free outcomes at 3 months, 16 (76.2%) successfully completed the diet for 2 years without seizure relapse. Furthermore, 9 (42.9%) of them have remained seizure-free over a mean follow-up period of 3 years and 10 months (range: 13 months to 7 years) after successful completion of the diet. Of the 7 patients who showed relapse seizures after completion of the diet, 1 patient became seizure-free with additional medication, 3 were lost to follow-up, and 3 patients ultimately underwent epilepsy surgery. In addition, of the 21 patients who remained seizure-free 3 months after diet initiation, 10 (47.6%) showed seizure-free outcomes even after completion of the KD. A schematic diagram of the long-term outcomes in these 47 patients is shown in Fig 1.

During administration of the KD, 2 patients stopped the diet as a result of hemorrhagic gastritis. Despite diet

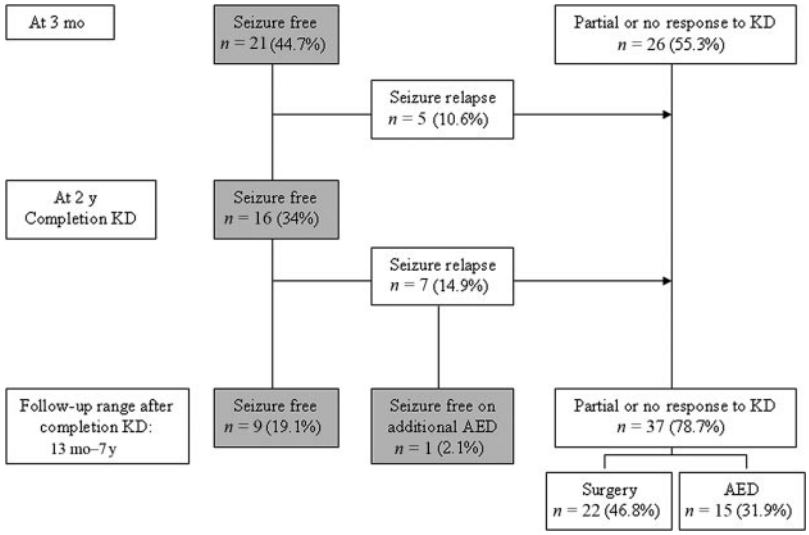

FIGURE 1
Flow diagram of short-term and long-term efficacy of the KD in intractable childhood epilepsy with focal MCD ($N = 47$).

intolerance in 5 patients, a reduction in seizure frequency of >50% was observed.

Outcomes of Surgical Treatment

Eventually, 22 patients, including 19 in whom seizures were not controlled completely during the KD and 3 patients who had relapsed seizures after successful completion of the KD, underwent surgical treatments. Only 2 patients had temporal lobe lesions; others had extratemporal (14 patients), multilobar (3 patients), or hemispheric (3 patients) lesions.

Of 22 patients who underwent epilepsy surgery, 13 (59.1%) obtained Engel class I outcomes, 5 (22.7%) obtained Engel class II outcomes, 2 (9.1%) obtained Engel class III outcomes, and 2 (9.1%) had no improvement during the mean ± SD follow-up period of 31.5 ± 26.2 months after epilepsy surgery (range: 8 months to 7 years). In the 22 patients, tissue pathologies were classified as MCD type 1 or type 2 in 18 patients and mild cortical dysplasia in 4 (Table 2). After surgery, no major complications occurred in those who had regional resections, but contralateral hemiparesis was seen in 3 patients who had hemispherec(o)tomy.

TABLE 2 **Surgical Treatment Outcomes of Patients With Focal MCD ($n = 22$)**

Parameter	*n* (%)
Surgical approach	
Temporal lobe resection	2 (9.1)
Extratemporal resection	14 (63.6)
Multilobar resection	3 (13.6)
Hemispherec(o)tomy	3 (13.6)
Engel classification (follow-up at 31.5 ± 26.2 mo)	
Seizure free (class I)	13 (59.1)
Rare seizure (class II)	5 (22.7)
Worthwhile reduction (class III)	2 (9.1)
No improvement (class IV)	2 (9.1)
Pathologic diagnosis	
MCD type 1 or 2	18 (81.8)
Mild cortical dysplasia	4 (18.2)

DISCUSSION

This study describes the experience of the KD in patients with intractable epilepsy and surgically remediable focal MCD. At 3 months after diet initiation, 21 (44.7%) patients became seizure-free. Sixteen (34%) patients successfully completed the diet, and 9 (19.1%) showed seizure-free outcomes even after completion of diet therapy to the time of the final follow-up (range: 13 months to 7 years). Of 21 patients who were seizure-free at 3 months after diet initiation, 10 (47.6%) remained seizure-free even after completion of diet therapy, including 1 patient who remained seizure-free with additional medication after a relapse.

Outcomes in our patients with focal MCD were superior to those of large prospective and retrospective studies of the conventional KD in patients with seizures of various causes.[10,15] An Italian group treated 7 patients (mean age: 8.2 years; range: 2.8–16.1) who had diffuse migrational disorders; at 9 months after the introduction of the diet, 4 of them experienced a decrease in seizure frequency between 50% and 90%.[16] Coppola et al[11] and Than et al[9] suggested that patients with MCD may respond particularly well to the diet. Biological evidence also supports good responses to the KD in patients with MCD. In suckling rats, the more immature the cerebral cortex is, the more it uses ketone bodies, instead of glucose, as an energetic substrate.[17,18] Most patients in this study had cortical dysplasia with variable extent and severity, and we could not differentiate the efficacy of the diet therapy according to specific types of MCD. We were also unable to find a significant difference in seizure outcomes in specific types of lesions.

Epilepsy surgery, whenever possible, is used in the treatment of intractable childhood epilepsy with focal MCD but does not always guarantee a favorable result.[7] In pediatric series, predominant surgical interventions are extratemporal or multilobar resections or hemispherec(o)tomies.[4] Seizure-free outcomes are less common in these patients than in those who undergo temporal resections.[7] The Cleveland Clinic's pediatric study

reported seizure-free outcomes in 54% of patients who had extratemporal or multilobar resection and in 78% of those who underwent temporal resections; results after hemispherectomy were intermediate (68%).[4] In our patients, of the 20 who had extratemporal or multilobar resection or hemispherectomy, 12 (60%) patients obtained Engel class I outcomes, a result similar to that of the Cleveland Clinic report.

In the administration of the KD, various complications occurred, but most were transient and could easily be managed by conservative treatments.[13,19] Even serious complications could be resolved after stopping the diet.[13] Contrary to the complications of diet therapy, we experienced sustained hemiparesis in 3 patients who had hemispherec(o)tomy. Because of the potential risks of sustained functional morbidity, surgical intervention is still challenging in most patients.

Twenty-seven (56%) of the patients in this study started the KD at an age younger than 36 months (the most compatible age for the KD). Seizure outcomes between younger and older children were similar, and the compliance to the KD was far better in younger children. Recent articles have demonstrated that considering its safety and efficacy, the early use of the KD seems to be a reasonable choice.[20,21] Successful surgical treatment of infants or younger children with focal MCD can provide complete seizure control and restore developmental progress as a result of the plasticity of the young brain.[5,6] Nevertheless, despite the gratifying results of early surgery, potential risks, such as hemodynamic instability, should be carefully considered in these young patients.[7,22]

CONCLUSIONS

Of the 47 patients in this study, in the 22 patients who underwent epilepsy surgery, 13 became seizure-free. In addition, by virtue of the KD, an additional 10 patients obtained seizure-free outcomes without epilepsy surgery. Resection of the focal MCD, if possible, remains the current treatment of choice in intractable epilepsy. Conversely, our results suggest that intractable childhood epilepsy with surgically remediable focal MCD may also respond favorably to the KD, and long-term seizure-free outcome can be expected especially for patients who become seizure-free at 3 months after the diet. Conclusively, the KD should be considered as early as possible and integrated with epilepsy surgery as part of a therapeutic strategy against refractory epilepsy as a result of focal MCDs.

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