The ketogenic diet is effective for refractory epilepsy due to acquired structural epileptic encephalopathy

Mel Michel Villaluz[1‡], Lysa Boissé Lomax[1‡], Trupti Jadhav[2],
J. Helen Cross[2,3], Ingrid E. Scheffer[1, 4, 5*]

[1] Epilepsy Research Centre, The University of Melbourne, Austin Health, Heidelberg, Victoria, Australia

[2] Neurosciences Unit, UCL Institute of Child Health, Great Ormond Street Hospital

[3] Young Epilepsy, London, UK

[4] Department of Paediatrics, Royal Children's Hospital, and the Florey Institute, Melbourne, Australia

[5] Florey Institute of Neuroscience and Mental Health

[‡] These authors contributed equally

[*] Corresponding author: Prof I.E. Scheffer, Austin Health, The University of Melbourne, Melbourne Brain Centre, 245 Burgundy Street, Heidelberg, VIC 3084, Australia.
Tel.: +61 39035 7344; fax: +61 39035 7037

E-mail address: scheffer@unimelb.edu.au

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ABSTRACT

Aim

Ketogenic diet (KD) therapies have proven efficacy for refractory epilepsy. There are many reports of their use in the genetic developmental and epileptic encephalopathies, however, little attention has been paid as to whether the diet is also effective in individuals with an acquired structural aetiology. We observed remarkable efficacy of the diet in two patients with hypoxic-ischaemic encephalopathy. We then analysed our cases with refractory structural epilepsies of acquired origin to characterise their response to the ketogenic diet.

Method

The classical KD was implemented with dietary ratios of 3:1 to 4.4:1. Seizure frequency at 1, 3, 6 months, 1 and 2 years was ascertained. A responder was defined as >50% seizure reduction compared to baseline.

Results

Seven of the nine (78%) patients were responders at 3 months.

Interpretation

Somewhat surprisingly we found that the KD was effective in patients with a developmental and epileptic encephalopathy due to an acquired structural aetiology. This cohort may not be routinely considered for the KD due to their structural and acquired, rather than genetic, basis. The KD should be considered early in the management of patients with acquired structural encephalopathies as it can improve seizure control with the potential to improve developmental outcome.

Key words: Ketogenic diet, developmental and epileptic encephalopathy, hypoxic ischemic encephalopathy, acquired structural aetiology

What this paper adds:

- The ketogenic diet was effective in children with epilepsy due to an acquired structural aetiology

Patients with severe epilepsy secondary to an acquired structural aetiology may have refractory seizures that are not surgically amenable, often in association with bilateral cortical involvement. Patients with structural brain lesions acquired in infancy such as hypoxic-ischemic encephalopathy (HIE), intraventricular haemorrhage (IVH), infections or birth trauma, are at high risk of developing refractory epilepsy.[1] In these patients, the management of refractory epilepsy remains extremely challenging despite the availability of multiple anti-epileptic drugs.

The ketogenic diet (KD) has been used in the treatment of refractory childhood epilepsy since the 1920's. It is a medically initiated high fat, low carbohydrate diet with demonstrated efficacy in many epilepsy syndromes, including epilepsy with myoclonic-atonic seizures (described by Doose), Lennox-Gastaut syndrome (LGS) and Dravet syndrome.[2,3] The KD is also the treatment of choice for two rare disorders of brain energy metabolism: glucose transporter 1 deficiency and pyruvate dehydrogenase deficiency.[4,5] Most studies of KD efficacy have focused on seizure types or epilepsy syndromes rather than specific aetiological subgroups. Two patients with HIE from our study of 61 patients on the KD were seizure free at six months.[6] This led to the hypothesis that patients with refractory epilepsy due to acquired structural encephalopathy may respond to the KD. Here, we analysed the responder rate in a collaborative cohort of patients with refractory epilepsy due to acquired structural epileptic encephalopathy.

METHOD

In the retrospective study, patients were referred to the KD clinics at Austin Health, Melbourne, Australia (IES) and Great Ormond Street Hospital for Children, London, UK (JHC). Children with a history of acquired neonatal or infantile structural lesions who developed refractory epilepsy were included. Refractory epilepsy was defined as failure to achieve seizure freedom after adequate trials of two or more suitable antiepileptic medications.[7] A developmental and epileptic encephalopathy was diagnosed by a paediatric neurologist on the basis of developmental impairment and frequent epileptic activity on EEG that was associated with slowing of development beyond that expected from the structural lesion alone.[8,9]

Patients underwent detailed clinical history and physical examination prior to initiating the diet. Diagnostic tests were performed for metabolic and renal conditions that would preclude patients from starting the KD. EEG and MRI brain studies were analysed. Seizures were classified and an epilepsy syndrome diagnosis made according to the 2010 ILAE classification.[8]

The KD was initiated using a modified Johns Hopkins protocol. A fat to carbohydrate and protein ratio of 3:1 to 4.4:1 was used to achieve the necessary level of ketosis. The dietary ratio, energy, and protein intake were adjusted in order to achieve desired ketone levels and maintain appropriate growth with minimal side effects. Urinary ketones were monitored twice daily with the goal of 8mM in the morning and 16mM at night. For patients younger than 5 years, blood ketone levels between 2.4 and 4.2 mM were sometimes used. Doses of concurrent anti-epileptic drugs were kept stable during the first three months of the diet at least.

Seizure diaries were completed for a 28-day period prior to commencement (baseline seizure frequency) and on the KD. The average daily seizure frequency was calculated for the 28-day period before each time point and compared to the average baseline daily seizure frequency. The primary outcome was the percentage change in seizure frequency at 1, 3, 6 months and 1 and 2 years (when data was available) compared to baseline. A responder was defined as a patient who achieved >50% reduction in seizure frequency.

This study was approved by the Austin Health Human Research Ethics Committee.

RESULTS

Nine patients with an acquired structural developmental and epileptic encephalopathy were recruited to the study (Table). All 9 patients were diagnosed with HIE, IVH or perinatal brain injury in the neonatal or infantile period. All consecutive patients with acquired structural brain injury included in the ketogenic diet programs of Austin Health and the Great Ormond Street Hospital for Sick Children between 2001 and 2010 were included. The clinical, EEG and imaging findings are described in the table. Median seizure onset was 12 months (range: 1 month to 4 years). All patients had

multiple seizure types with daily frequencies ranging from five to innumerable seizures. Intellectual disability was profound in 7 patients and moderate in two. All patients had cerebral palsy: spastic quadriplegia in 7, spastic diplegia in 1 and hemiplegia in 1. Neuroimaging showed variable degrees of brain injury including widespread cortical damage, white matter gliosis, and periventricular leukomalacia.

Three months following KD initiation, 7/9 (78%) were responders and all patients showed some improvement. At 6 months post-initiation, 6/7 (86%) patients who remained on the diet were responders. Three patients were seizure-free, and two had reductions >94%. After one year, 6/6 patients on the diet were responders with three seizure-free, and two had >90% seizure reduction. After two years, all five patients remaining on the diet were responders including 3 seizure free and two with 70% or 95% reduction.

Subjective improvements in cognition were documented even with minimal effect on seizure frequency or even when the patient later discontinued the diet. Families observed increased alertness, vocalization, improved behaviour and subtle developmental gains in all children. The reason for discontinuing the KD in 4 cases was that the child refused the diet. Three of the nine children had percutaneous endoscopic gastrostomies. No child was weaned due to side effects such as weight loss or renal calculi.

DISCUSSION

Acquired structural causes of encephalopathy have an increased risk of epilepsy and other neurological sequelae. Neonates with HIE or meningitis have a risk of epilepsy of around 12%.[1] The seizure disorder is often refractory and may cause a epileptic encephalopathy that impacts on developmental progress beyond that caused by the structural pathology alone. To our knowledge, this is the first study to specifically focus on the effectiveness of the KD in patients with acquired structural epileptic encephalopathy.

The KD is a well-recognized and effective treatment for refractory childhood epilepsy.[2,10] In particular, it is a highly effective treatment for genetic developmental and epileptic encephalopathies such as epilepsy with myoclonic-atonic seizures and

Dravet syndrome.[11] In Dravet syndrome, responder rates of 65% are reported.[12,13] In epilepsy with myoclonic-atonic seizures, 55% (6/11) of patients were observed to have >50% seizure reduction at 18 months, with seizure freedom in 2/11 patients.[14] We found a striking responder rate of 78%, although our sample size is small. This is not dissimilar to genetic structural epilepsies, such as tuberous sclerosis where, in one study, 11/12 (92%) patients had a >50% response rate.[15] Efficacy has also been established in malformations of cortical development. A Korean study found that 29/47 patients were responders after three months on the diet.[16] Lennox-Gastaut syndrome can occur in the setting of both genetic and acquired structural aetiologies; Lemmon and colleagues found that 6/25 patients achieved >90% seizure reduction.[3] Although some patients with lesional epilepsy are epilepsy surgery candidates, in many cases the abnormalities are too extensive to be surgically amenable. For such patients with devastating epilepsy, the KD may be a worthwhile therapeutic option.

Here, 7/9 (78%) patients with an acquired structural aetiology showed >50% response at 3 months. At 2 years, 5/5 patients who remained on the KD were responders. If the patients who stopped the diet early are included, this is still a responder rate of 5/9 (55%). This responder rate is considerably greater than that observed in our broader study of 61 patients with refractory epilepsy due to genetic, structural and unknown aetiologies who had an overall 2 year responder rate of data of 14%.[6] This suggests that patients with acquired structural aetiologies may be particularly responsive to the KD. Studies with a larger sample size are required to confirm this positive response.

Interestingly, the families of our patients remarked on significant gains in development and quality of life. Most notably, alertness, calmness and developmental progress were seen, as documented previously.[17] It is not known whether these behavioural effects are due to decreased seizure frequency or to the ketosis. Even our patients with a minimal change in seizure frequency experienced behavioural and developmental improvements, often continuing after dietary cessation.[18] While these parental observations are promising, we acknowledge that such reports are likely to be subject to bias. Responses are often noted in the placebo arm of placebo-controlled studies, and are even more prominent in paediatric than adult trials.[19] It would be ideal to have objective assessments of the cognitive and behavioural changes, although cognitive gains are likely to be very subtle in profoundly impaired patients.

At first glance, the attrition rate of patients on the KD in our study may seem high yet careful analysis suggests this is not the case. At 3 months, all of our children were still on the KD which compares favourably with the attrition rate in our previous studies of 21% (13/61) (10) and 26% (19/73).[6,10] The remainder of the follow-up rates (6 months to 2 years) were similar to our previous study confirming that patients with acquired structural encephalopathy find the diet at least as efficacious as other groups.[6] In four patients, the KD was stopped as the patient refused the diet. Given the efficacy of the KD in this population, a gastrostomy may be worth considering if it renders the patient seizure-free and improves the quality of life for the patient and their family.

There has been extensive research into the multiple mechanisms underlying the efficacy of the KD.[20] Recent interest has highlighted that the epigenetic machinery may be modified through metabolic intervention.[21] Experimental acquired epilepsy models have shown genome-wide changes in DNA methylation with aetiology-dependent epigenetic signatures.[22] Thus, the KD may affect methylation patterns affecting gene expression, and thereby influence seizure susceptibility in individuals with acquired structural epilepsy. The increasing awareness of anti-inflammatory effects in anti-epileptic therapies is also likely to be relevant to the efficacy of the KD in patients with epilepsy due to an acquired structural aetiology.[23] The KD decreases proinflammatory cytokine levels after an immune challenge through multiple processes and molecular targets. These include an increase in polyunsaturated fatty acids,[24] which block epileptiform activity on in *in vivo* and *in vitro* seizure models, as well as effects on mitochondrial function.[25]

We report a series of refractory patients with acquired structural epileptic encephalopathy with impressive responses to the KD. Additional benefits, such as increased alertness, improved motor development and behaviour, were apparent. The role of the KD early in the treatment algorithm of children with acquired neonatal and infantile cerebral injury should be considered. Earlier seizure control in this highly refractory population has the potential to improve prognosis and quality of life for the patient and their family.

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Disclosure of Conflicts of Interest

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. All co-authors have been substantively involved in the study and the preparation of the manuscript. No undisclosed groups or persons had a have had a primary role in the preparation of this manuscript. All co-authors have seen and approved the submitted version of the paper and accept responsibility for its content.

Dr. Scheffer has served on scientific advisory boards for UCB and Janssen-Cilag EMEA; may accrue future revenue on pending patent WO61/010176 (filed: 2008): Therapeutic Compound; has received speaker honoraria from Athena Diagnostics, UCB, GSK, Biocodex, and Janssen-Cilag EMEA; and has received funding for travel from Athena Diagnostics, UCB, Biocodex, GlaxoSmithKline, and Janssen-Cilag EMEA.

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The remaining authors have nothing to disclose.

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Table 1. Clinical data of patients with acquired structural epileptic encephalopathy and their response to the ketogenic diet

Patients	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Age at study and gender	4y M	18y M	18y F	13y M	15y M	17y F	12y F	13y F	15y M
Aetiology	HIE	HIE	Prematurity (23w 6d) IVH and hydrocephalus	HIE	Prematurity with brain injury (32w, septicaemia, exchange transfusion)	Prematurity (34w) with brain injury	HIE post-bacterial meningitis	HIE post-bacterial meningitis	HIE
Age of Brain Injury	Birth	Birth	IVH: Birth Hydrocephalus:2m	Birth	Birth	Birth	8 months	10 months	Birth
Age at seizure onset	3m	6m	2y 6m	12m	18m	4y	12m	10m	1m
Seizure Types	GTC Tonic Focal Absence Infantile spasms	GTC Tonic Focal Absence Myoclonic Gelastic	GTC Focal Apnoeic events	GTC Tonic Atypical absence Myoclonic Infantile spasms	GTC Tonic Atonic Atypical absence	GTC Tonic Absence Myoclonic NCSE	Tonic Focal Infantile spasms	Focal (in clusters)	GTC Tonic Drop attacks Atypical absence Myoclonic

EEG Findings	Multifocal 3-4Hz GSW	2Hz GSW PSW GPFA	Bifrontal SW GSW	Hypsarrhythmia Multifocal Ictal: myoclonic seizures	Multifocal Ictal: tonic seizure	Multifocal	Multifocal 2-3Hz SW	Multifocal Ictal: myoclonic seizures	Multifocal 2Hz GSW
MRI brain	Periventricular leukomalacia Ulegyria	Extensive bilateral encephalomalacia	CT: Bifrontal gliosis and dystrophic calcification VP shunt	Generalized cerebral atrophy Paucity of white matter	Generalized atrophy, mild cortical gliosis	Mild periventricular leukomalacia	Widespread cortical damage	Widespread encephalomalacia	CT: Extensive bilateral ischemic gliosis
Co-morbidities	Profound ID Spastic quadriplegia	Profound ID Spastic quadriplegia PEG	Profound ID Acquired Hydrocephalus Spastic quadriplegia PEG	Profound ID Cortical visual impairment Spastic quadriplegia PEG	Moderate ID Spastic quadriplegia	Moderate ID Spastic diplegia	Profound ID Mild right hemiplegia Cortical visual impairment	Profound ID Spastic quadriplegia Cortical visual impairment	Profound ID Microcephaly Cortical visual impairment Spastic quadriplegia
AEDs at KD initiation	LEV TPM	LTG VPA	CBZ CZP TPM	CLB LTG TPM	CLB PB VGB	ETH LTG LEV VPA	LTG VPA	LTG VPA	CLB LEV
Previous AEDs	CBZ	CBZ CZP PB	DZP Paraldehyde PHT TGB	ACTH LEV PT Prednisolone VPA	CBZ LEV PHT TPM VPA	CLB TPM	Prednisolone VGB	CBZ PB PHT	CBZ ETH TPM VPA
Age KD initiated	1y 7m	15y 8m	8y 8m	4y	5y	9y 6m	3y 6m	5y	9y
KD ratio	3:1	4.4:1	4:1	4:1	4:1	4:1	4:1	4:1	4:1
Seizure Frequency prior to	All types: multiple/day Focal: 80-100/ d	All types: multiple/d	GTC: 2-3x/w Focal: Frequent/d	All types: 74 /d	All types: 16/d GTC: few/w Tonic: 5-6/d	All types: 33/d Tonic: 3-4/d	All types: 9 /d Tonic: 1	9 focal clusters/day	Tonic: 20/d Myoclonic: multiple/d

KD (mean daily seizures)		Tonic: 5-10/ d	Apnoea in infancy		Absence: 10/d	Absence: frequent daily In NCSE 50% of time.	cluster/d Focal: 6-8/d		Atypical absence: multiple/d

KD Response									
1 month	> 85% reduction	> 50% reduction	>95% reduction	Fewer GTC	Not quantified	Not quantified	50% reduction	Unchanged frequency but shorter duration	Not quantified
3 months	> 90% reduction	>95% reduction	Seizure free	60% reduction	86% reduction	48% reduction	54% reduction	29% reduction	78% reduction
6 months	Seizure Free	Seizure Free	Seizure free	58% reduction	94% reduction	27% reduction	97% reduction	Discontinued at 3 months	Discontinued at 3 months
1 year	Seizure free	90% reduction	Seizure free	68% reduction	98.5% reduction	Discontinued at 6 months	Seizure free	-	-
2 years	Seizure free (1 episode focal status 22m on diet)	95% reduction	Seizure free	70% reduction	Discontinued at 12 months	-	Seizure free	-	-
Development and behaviour on KD	More alert Calm Happy	More alert	More alert Vocalizing Sitting up without support	Calm Happy Developmental improvement Vocalizing	More alert Marked cognitive improvement	More alert	More alert Marked cognitive improvement More active	Mild cognitive improvement	Mild cognitive improvement

	Increased purposeful movement		Hand clapping		Learned new colours				
Patient follow-up									
Current age	9y	24y	24y	18y	20y	23y	17y	18y	21y
Follow-up	Still on KD	Died in 2014 (cause of death unknown)	Lost to follow-up	Still on KD	Weaned from diet after 3years; thereafter lost to f/up	Lost to followup	Weaned from KD after 2 years; no further follow-up	-	-

Legend: AED's – Antiepileptic drugs; CBZ – Carbamazepine; CLB – Clobazam; CZP – Clonazepam; CT – Computed tomography; d – days; DZP – Diazepam; EEG – Electroencephalogram; ETH –Ethosuximide; F – female; GTC – Generalised tonic clonic seizures; GPFA – generalized paroxysmal fast activity; GSW – generalized spike and wave; HIE – Hypoxic ischemic encephalopathy; ID – Intellectual disability; IS – Infantile spasms; KD – Ketogenic diet; LEV- Levetiracetam; LTG – Lamotrigine; M – male; m – months; NCSE – Non-convulsive status epilepticus; PB – Phenobarbitone; PEG – percutaneous endoscopic gastrostomy; PHT – Phenytoin; PSW – polyspike and wave; TGB – Tiagabine; TPM – Topiramate; VGB - Vigabatrin, VPA – Sodium Valproate; w – weeks; y – years