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The ketogenic diet is effective for refractory epilepsy associated with acquired structural epileptic encephalopathy

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AIM Ketogenic diet 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 ketogenic diet was implemented with dietary ratios of 3:1 to 4.4:1. Seizure frequency at 1 month, 3 months, 6 months, 1 year, and 2 years was ascertained. A responder was defined as greater than 50 per cent seizure reduction compared to baseline.

RESULTS Seven of the nine patients were responders at 3 months.

INTERPRETATION Somewhat surprisingly we found that the ketogenic diet 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 ketogenic diet because of their structural and acquired, rather than genetic, basis. The ketogenic diet 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.

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What this paper adds

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

[main text]

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, intraventricular haemorrhage, 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 antiepileptic drugs.

The ketogenic diet has been used in the treatment of refractory childhood epilepsy since the 1920s. 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, and Dravet syndrome.[2,3] The ketogenic diet 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 ketogenic diet efficacy have focused on seizure types or epilepsy syndromes rather than specific aetiological subgroups. Two patients with hypoxic-ischemic encephalopathy from our study of 61 patients on the ketogenic diet were seizure free at 6 months.[6] This led to the hypothesis that patients with refractory epilepsy associated with an acquired structural encephalopathy may respond to the ketogenic diet. Here, we analysed the responder rate in a collaborative cohort of patients with refractory epilepsy associated with an acquired structural epileptic encephalopathy.

METHOD

In this retrospective study, patients were referred to the ketogenic diet 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 electroencephalogram 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 before initiating the diet. Diagnostic tests were performed for metabolic and renal conditions that would preclude patients from starting the ketogenic diet. Electroencephalogram and magnetic resonance imaging brain studies were analysed. Seizures were classified and an epilepsy syndrome diagnosis made according to the 2010 International League Against Epilepsy classification.[8]

The ketogenic diet 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 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 2.4mM and 4.2mM were sometimes used. Doses of concurrent antiepileptic drugs were kept stable during the first 3 months of the diet at least.

Seizure diaries were completed for a 28-day period before commencement (baseline seizure frequency) and on the ketogenic diet. 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 month, 3 months, 6 months, 1 year, and 2 years (when data was available) compared to baseline. A responder was defined as a patient who achieved greater than 50 per cent 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 I). All 9 patients were diagnosed with hypoxic-ischemic encephalopathy, intraventricular haemorrhage, 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, electroencephalogram, and imaging findings are described in Table I. 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 seven patients and moderate in two. All patients had cerebral palsy; seven had spastic quadriplegia, one had spastic diplegia, and one had hemiplegia. Neuroimaging showed variable degrees of brain injury including widespread cortical damage, white matter gliosis, and periventricular leukomalacia.

Three months after ketogenic diet initiation, seven out of nine patients were responders and all patients showed some improvement. At 6 months postinitiation, six out of seven patients who remained on the diet were responders. Three patients were seizure-free, and two had reductions less than 94 per cent. After one year, six out of six patients on the diet were responders with three seizure-free, and two had less than 90 per cent seizure reduction. After two years, all five patients remaining on the diet were responders including three seizure-free and two with 70 per cent or 95 per cent 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 ketogenic diet in four cases was that the child refused the diet. Three of the nine children had percutaneous endoscopic gastrostomies. No child was weaned because of 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 hypoxic-ischemic encephalopathy or meningitis have a risk of epilepsy of around 12 per cent.[1] The seizure disorder is often refractory and may cause an 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 ketogenic diet in patients with acquired structural epileptic encephalopathy.

The ketogenic diet is a well-recognised 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 per cent are reported.[12,13] In epilepsy with myoclonic-atonic seizures, 55 per cent (6/11) of patients were observed to have greater than 50 per cent seizure reduction at 18 months, with seizure freedom in two out of 11 patients.[14] We found a striking responder rate of 78 per cent, although our sample size is small. This is not dissimilar to genetic structural epilepsies, such as tuberous sclerosis where, in one study, 11 out

of 12 patients had a greater than 50 per cent response rate.[15] Efficacy has also been established in malformations of cortical development. A Korean study found that 29 out of 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 et al. found that 6 out of 25 patients achieved greater than 90 per cent 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 ketogenic diet may be a worthwhile therapeutic option.

Here, seven out of nine patients with an acquired structural aetiology showed greater than 50 per cent response at 3 months. At 2 years, five out of five patients who remained on the ketogenic diet were responders. If the patients who stopped the diet early are included, this is still a responder rate of 5 out of 9. This responder rate is considerably greater than that observed in our broader study of 61 patients with refractory epilepsy caused by genetic, structural, and unknown aetiologies who had an overall 2-year responder rate of data of 14 per cent.[6] This suggests that patients with acquired structural aetiologies may be particularly responsive to the ketogenic diet. 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 because of 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 ketogenic diet 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 ketogenic diet which compares favourably with the attrition rate in our previous studies of 21 per cent (13/61) and 26 per cent (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 ketogenic diet was stopped as the patient refused the diet. Given the efficacy of the ketogenic diet 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 ketogenic diet.[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 ketogenic diet 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 antiepileptic therapies is also likely to be relevant to the efficacy of the ketogenic diet in patients with epilepsy associated with an acquired structural aetiology.[23] The ketogenic diet 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 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 ketogenic diet. Additional benefits, such as increased alertness, improved motor development, and behaviour, were apparent. The role of the ketogenic diet 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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Dr Scheffer has served on scientific advisory boards for UCB and Janssen-Cilag Europe, Middle-East and Africa (EMEA); may accrue future revenue on pending patent WO61/010176 (filed: 2008): Therapeutic Compound; has received speaker honoraria from Athena Diagnostics, UCB, GlaxoSmithKline, 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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Table I: 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 sex	4y M	18y M	18y F	13y M	15y M	17y F	12y F	13y F	15y M
Aetiology	HIE	HIE	Preterm (23w 6d) IVH and hydrocephalus	HIE	Preterm with brain injury (32w, septicaemia, exchange transfusion)	Preterm (34w) with brain injury	HIE postbacterial meningitis	HIE postbacterial meningitis	HIE
Age of brain injury	Birth	Birth	IVH: Birth Hydrocephalus :2mo	Birth	Birth	Birth	8mo	10mo	Birth
Age at seizure onset	3mo	6mo	2y 6mo	12mo	18mo	4y	12mo	10mo	1mo
Seizure types	GTC Tonic Focal Absence	GTC Tonic Focal Absence	GTC Focal Apnoeic events	GTC Tonic Atypical absence	GTC Tonic Atonic Atypical	GTC Tonic Absence Myoclonic	Tonic Focal Infantile spasms	Focal (in clusters)	GTC Tonic Drop attacks Atypical

	Infantile spasms	Myoclonic Gelastic		Myoclonic Infantile spasms	absence	NCSE			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 encephaloma lacia	CT: Bifrontal gliosis and dystrophic calcification VP shunt	Generalised cerebral atrophy Paucity of white matter	Generalised atrophy, mild cortical gliosis	Mild periventricular leukomalacia	Widespread cortical damage	Widespread encephalomalacia	CT: Extensive bilateral ischemic gliosis
Comorbidities	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 7mo	15y 8mo	8y 8mo	4y	5y	9y 6mo	3y 6mo	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 before KD (mean daily seizures)	All types: multiple/day Focal: 80–100/d	All types: multiple/d Tonic: 5–10/d	GTC: 2–3x/w Focal: Frequent/d Apnoea in infancy	All types: 74/d	All types: 16/d GTC: few/w Tonic: 5–6/d Absence: 10/d	All types: 33/d Tonic: 3–4/d Absence: frequent daily In NCSE 50% of time	All types: 9 /d Tonic: 1 cluster/d Focal: 6–8/d	9 focal clusters/day	Tonic: 20/d Myoclonic: multiple/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 Increased purposeful movement	More alert	More alert Vocalizing Sitting up without support Hand clapping	Calm Happy Developmental improvement Vocalizing	More alert Marked cognitive improvement Learned new colours	More alert	More alert Marked cognitive improvement More active	Mild cognitive improvement	Mild cognitive improvement

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 follow-up	Lost to follow-up	Weaned from KD after 2 years; no further follow-up	–	–

Y, years; M, male; F, female; HIE, hypoxic-ischemic encephalopathy; IVH, intraventricular haemorrhage; w, weeks; d, days; mo, months; GTC, generalised tonic clonic seizures; NCSE, non-convulsive status epilepticus; EEG, electroencephalogram; GSW, generalised spike and wave; PSW, polyspike and wave; GPFA, generalised paroxysmal fast activity; SW, spike wave; MRI, magnetic resonance imaging; CT, computed tomography; VP, ventriculoperitoneal; PEG, percutaneous endoscopic gastrostomy; KD, ketogenic diet; ID, intellectual disability; AEDs, antiepileptic drugs; LEV, levetiracetam; TPM, topiramate; LTG, lamotrigine; VPA, sodium valproate; CZP, clonazepam; CBZ, carbamazepine; CLB, clobazam; PB, phenobarbitone; VGB, vigabatrin; ETH, ethosuximide; DZP, diazepam; PHT, phenytoin; TGB, tiagabine; ACTH, adrenocorticotropic hormone.

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