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Case Report

Ketogenic diet in Zambia: Managing drug-resistant epilepsy in a low and middle income country

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ABSTRACT

Globally, drug-resistant epilepsy affects one third of people living with epilepsy. With limitations in treatment options for refractory epilepsy in resource-limited regions, ketogenic diet therapy is an important option to consider. Utilizing the 2015 International League Against Epilepsy recommended minimum requirements for ketogenic diet therapy, three male children with refractory epilepsy, aged 2.5, 6.5 and 10 years, were initiated on the classical ketogenic diet using locally available food in August 2017 at University Teaching Hospitals-Children's Hospital in Lusaka, Zambia, through partnership with the Epilepsy Program at Boston Children's Hospital in the United States. Following successful initiation in all three children, the diet was discontinued in the 10-year-old due to difficulties complying with the diet. The youngest child demonstrated an over 50% seizure reduction and gained developmental milestones. The third child achieved seizure freedom and showed marked improvement in behaviour. This pilot demonstrates the feasibility of ketogenic diet as an important therapeutic option for refractory epilepsy in Zambia. Given the limitations in treatment choices and medication accessibility, dietary therapy offers an alternative management strategy in our setting. Collaboration with an established ketogenic diet centre contributes to a successful program.

1. Introduction

Over 80% of the 50 million people affected by epilepsy globally live in low- and middle-income (LMIC) countries, where the treatment gap – those with active epilepsy not on appropriate treatment – is the highest, ranging from 75 to 90% [1,2]. In Zambia, it is around 80–90% [3] and despite efforts to improve neurologic care, a large burden of disease persists [4,5]. This is due to a multitude of factors including few specialists, geographic barriers, and limited diagnostics; however, inconsistent availability of antiseizure medications (ASMs) remains one of the most prominent issues [6].

Drug-resistant epilepsy (DRE), defined as failure to respond to two or more appropriately chosen, adequately dosed, and tolerated ASMs, is an indication for non-pharmacologic management strategies such as surgery, neuromodulation, and ketogenic diet (KD) [7]; and in high resource regions, it is considered standard of care. In LMIC, however, resource constraints limit non-pharmacologic treatment options for DRE. Despite the growing number of neurosurgery programs and improvements in regional collaborations in sub-Saharan Africa (SSA), surgical options remain few due to poor infrastructure, inability to provide appropriate post-operative care, limited neuroimaging capacity, and when available, high costs.

The KD, a low carbohydrate, high fat and controlled protein diet, is an effective therapeutic option for DRE in children, with wide use in most specialized paediatric epilepsy centres across the world [8,9]. Its use in childhood epilepsies is associated with complete seizure control and more than 50% reduction in seizures in up to 15.6% and 33% of children respectively [10]. Improvement in behaviour, cognitive functioning and decreased anxiety and mood problems has also been reported [11]. Despite discussions amongst providers in LMIC about the diet as a potential therapy, including publication from The International League

Abbreviations: ASM, anti-seizure medication; BCH, Boston Children's Hospital; HIC, high-income countries; ILAE, International League Against Epilepsy; KD, ketogenic diet; LMIC, low- and middle-income countries; RE, refractory epilepsy; SSA, Sub Saharan Africa; UTH-CH, University Teaching Hospitals-Children's Hospital; VNS, vagus nerve stimulation.

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Against Epilepsy (ILAE) in 2015 regarding the minimum requirements for KD services in resource-limited settings in 2015 [12], there has been little reported use, and it is not routinely offered as standard of care in most countries in SSA. One major reason for this includes absence of a clear implementation strategy that is feasible within the resource constraints of the region, where there is a limitation of specialists and laboratory monitoring.

We describe here a practical and safe implementation strategy, adapted from the ILAE 2015 guidelines, utilized with success at a tertiary care centre in SSA. This program demonstrates avenues for success and aspects of the ILAE guidelines which require flexibility in consideration for use of KD in Africa and is the first reported use of the KD in Zambia.

2. Methods

2.1. Study site

The University Teaching Hospitals- Children's Hospital (UTH-CH) in Lusaka, Zambia is the main paediatric referral hospital in Zambia, admitting 20,000 children annually to the 370-bed facility and approximately 1200 annual outpatient neurology visits. Despite UTH-CH having the most consistently available antiseizure medication (ASM) in the country, this remains limited, with carbamazepine, phenobarbital, and valproic acid being the most consistently available drugs, and with limited supplies of lamotrigine, clonazepam, and levetiracetam.

After discussions between UTH-CH and BCH regarding the feasibility of KD within our setting, the specialized KD team from BCH, consisting of an epileptologist (AB) and dietician (ST) travelled to Zambia and provided onsite workshops for the local medical team consisting of one child neurologist from Italy residing in Zambia, two Zambian pediatricians and two nutritionists.

2.2. Study participants

Three children across different social economic strata were identified as appropriate candidates based on knowledge of underlying etiology, due to our limitations in performing a full laboratory metabolic assessment and caregiver willingness to participate (see Table 1). Extensive counselling was conducted with each family explaining the shift from carbohydrates to fat prior to diet initiation. Caregivers were required to sign consent forms and verbally express their understanding of the process.

The nutrition team identified easily accessible and affordable local foods for each family based on their individual household income. Recipes using these foods were designed for each child based on their prescribed ketogenic ratio and calculated daily caloric requirement.

2.3. Diet implementation

Participants were admitted to the hospital for initiation of the classical KD. Baseline laboratory studies as per ILAE guidelines were performed, with the exception of serum acylcarnitine and free carnitine levels as local testing were unavailable at the time of the trial. No fasting period was observed. The diet initiation for the first two children was performed by both teams, while the third child was initiated on the diet independently (with remote consultation) by the local team.

While in the hospital, the nutrition team educated the parents on appropriate foods and fluids, preparation of the different meals and post discharge expectations. Monitoring for ketosis and immediate side effects (i.e. dehydration, hypoglycaemia and worsening seizures) of diet initiation was done by monitoring the general wellbeing, alertness and vital signs (pulse and respiratory rate). Daily urinalysis, serum ketones and blood glucose levels (using a bedside keto-/glucometer) were performed. Participants were discharged from the hospital after 72 h. Each child received locally sourced multivitamins, calcium supplements and levo-carnitine on discharge, confirmed sufficient for use by the nutrition team. Efforts were made to find the least expensive supplements to enhance sustainability of the program.

2.4. Follow-up

Outpatient follow-up continued for one year by the local team. Measurement of growth parameters, serum ketone levels, review of seizure response and medication and diet adjustments was done at every review.

Table 1
Characteristics of children initiated on the ketogenic diet.

	Child one	Child two	Child three
Sex,Age (years)	Male,2.5 years	Male,6.5 years	Male,10 years
Seizure onset	9 months	2 years	4.5 years
Seizure type	Epileptic spasms, atonic seizures and myoclonic seizures	Atypical absence, atonic seizures, frequent episodes of non-convulsive status epilepticus	Tonic, atypical absence
Frequency at time of initiation	Up to 15 clusters of spasms and 3-5 atonic seizures per day	1–2 atonic seizures per day	1–5 per day
Etiology	Genetic-Trisomy 21	Symptomatic- history of encephalitis at age of 2 years	Perinatal injury
Antiseiziure medication at initiation of KD	levetiracetam, valproic acid, lamotrigine	valproic acid, lamotrigine, clonazepam, levetiracetam	valproic acid, lamotrigine, clonazepam
Pre-KD EEG	Diffuse encephalopathy multifocal, generalized, and polyspikes; consistent with hypsarrhythmia pattern primarily in sleep with a relatively better waking record	Diffuse encephalopathy; multifocal spikes	Diffuse encephalopathy; slow spike-and-wave with multifocal spikes and four electroclinical tonic seizures out of sleep captured
Family/parent characteristics			
• Caregivers level of education	University	Primary school	Primary school
• Monthly household income	Above K5,000/$300	K1,000- K5,000/ $52-$300)	Below K1000/$52
• Members in household	Father, mother, two elder sisters	Father, mother, three elder brothers	Father, mother, two brothers
• Family diet provider	Mother, sisters and nanny	Mother and elder brother	Mother

See Fig. 1 for conceptual framework of program development.

Ethical approval for this trial was obtained from the University of Zambia bio-medical research ethics committee (UNZABREC).

3. Results

All the participants achieved ketosis within 48–72 h of initiation on their respective initial ratios.

Child one, a male child aged 2.5 years with Trisomy 21 and epileptic encephalopathy was initiated on the KD at a ratio of 1.5:1. He was having daily, multiple seizures of different semiology (epileptic spasms, atonic seizures and myoclonic seizures) and was significantly delayed in his development prior to KD initiation, maintained on 4 ASMs and multiple short steroid courses. With the diet, he has achieved greater than 50% reduction in seizure activity and progressed developmentally, primarily in gross motor domain. He remains on a ratio of 3:1, with no adjustments to his ASMs made since initiation; of note, previously utilized steroid pulses for acute exacerbation of seizures have not been required.

Child two, a male child aged 6.5 years with DRE secondary to encephalitis at age 2 years associated with cognitive impairment, was initiated on the KD at a ratio of 2:1. Prior to KD initiation, he was being followed up for DE complicated by frequent episodes of non-convulsive status epilepticus, despite high dosing of four ASMs, notably with variable adherence due to cost and access. While on the KD, he achieved complete seizure control and showed marked improvement in behaviour and has been maintained on a ratio of 2.5:1. Since diet initiation, he has also been successfully been weaned off one ASM and is in the process of being weaned off a second, with better levels of alertness and overall improved adherence to therapy, both diet and medication.

Child three, a 10-year-old male with RE consistent with Lennox–Gastaut syndrome following probable perinatal injury. Baseline seizure frequency was 1–5 tonic seizures per day while on three ASMs. He was initiated on the KD at a ratio of 2:1. Initial follow-up in the trial three-month period revealed an initial improvement in seizure frequency, down to 3–4 per week, but within one month, he appeared to return to baseline frequency. Investigation revealed inconsistent ketosis once discharged. The local team worked on diet strategies, including increased ratio, but found no improvement, and subsequently mother reported adherence difficulties due to lack of compliance at school and mother's work commitments preventing direct supervision at home. Diet was withdrawn after three months without complication; patient remains stable on three ASMs.

4. Discussion

The KD aims to optimize seizure control and enhance quality of life, while maintaining adequate nutrition necessary for a child's growth and development. Our pilot trial demonstrated results broadly as expected with one child seizure free and able to taper two anticonvulsant medications, one child with benefit but not seizure-free and one child discontinuing diet at 3 months, the usual duration to establish efficacy and/or tolerability. Both successful cases had additional gains, with one showing developmental progress, and the other behavioural improvements. These changes are likely attributable to a variety of factors: decreased seizure numbers, decreased medication burden and possibly other effects of KD on brain energy metabolism.

In SSA, the only reported well-established program for KD is currently in South Africa [13]. Outside of South Africa, a single case-report from Ghana on use of KD has been published, describing implementation by a visiting team and with ketogenic formula, thus limiting applicability to other settings in the region. We demonstrated a more sustainable approach, utilizing visiting experts to provide training for local medical and nutrition staff. This was demonstrated by the local

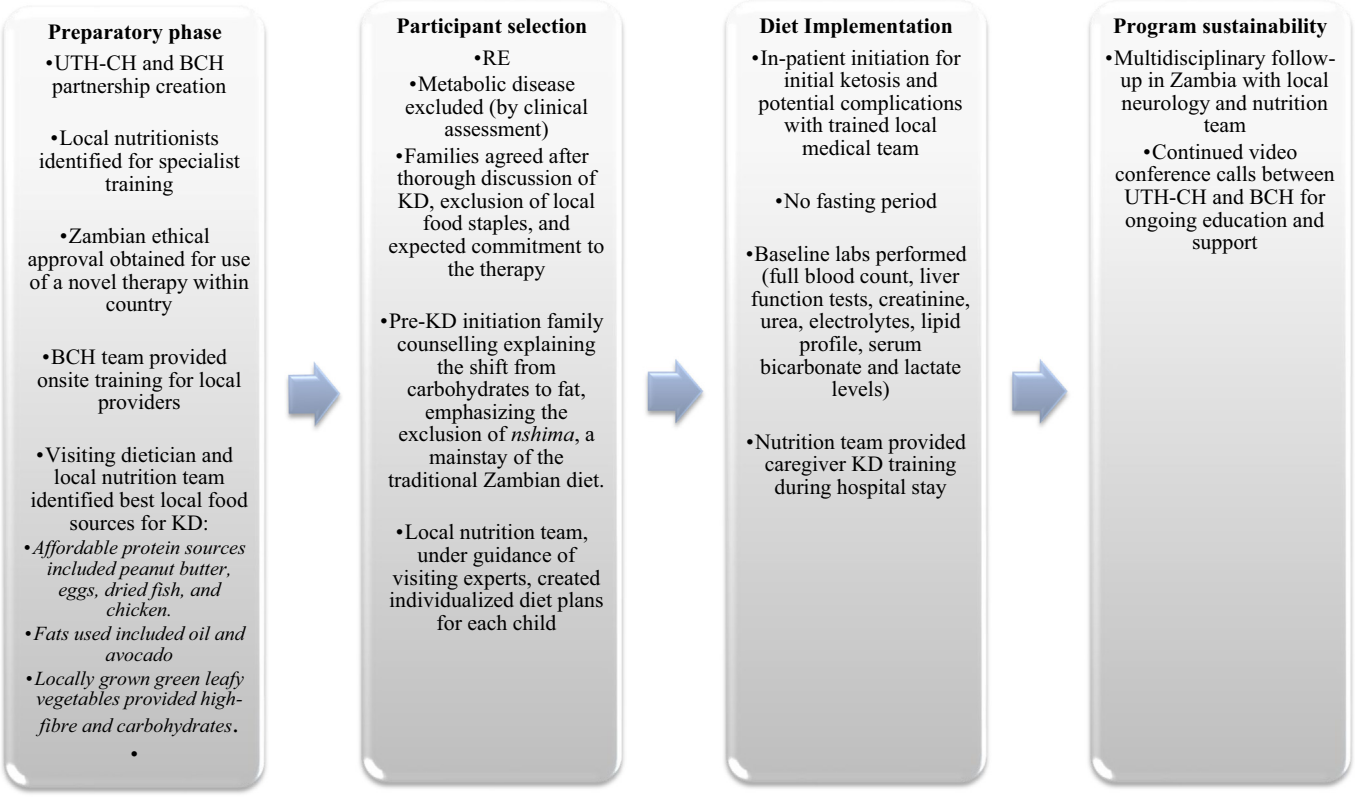

Fig. 1. Adaptation of the ILAE's recommended minimum requirements for KD implementation 1
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team's independent initiation of child 3, with only remote support from the visiting team. Long-term sustainability was further demonstrated by the Zambian team's ability to continue long-term management of each the children, titrating the diet as needed. In addition, local, easily accessible and affordable food was identified by the local nutritionists in collaboration with the expert visiting KD dietician. Cultural understanding (regarding the centrality of and emotional attachment to *nshima* in the local diet) was critically provided by the local team.

The ILAE recommendations include a "mandatory" registered dietician in the local team, especially for the classic KD diet. We were unable to provide this level of nutritional support. However, with institutional support and two highly motivated nutritionists, the visiting registered dietician provided training and supervision on obtaining a nutritional history, selection of food, weighing of food, calculation of food ratios and adjustment of ratios according to the participant's clinical response. With this strong training program and ongoing remote support, it is our feeling that our nutritionists are now well equipped to support the KD program at our centre with a high level of competence. The UTH program/team is further supported by monthly video conferences and annual site visits to discuss the participants and consider potential new candidates for diet treatment. On-site training saved the time and expense involved in the local team travelling to visit a well-established centre.

Initiation of a KD in the setting of some metabolic disorders (e.g. fatty acid oxidation) can cause serious systemic and potential neurologic injury. Inability to exclude metabolic disorders in children with RE in whom a clear etiology has not been established is a barrier to considering KD in this region where diagnostic availability is limited. While we acknowledge that this is a challenge for broad use in the LMIC, we demonstrated that with careful clinical assessment, the current ILAE guidelines could be adapted in a safe manner for this setting. Regardless, KD will not be an option for some children where metabolic disease cannot be excluded.

Widespread use of KD in epilepsy treatment faces the challenge of costing approximately twice that of the traditional local diet. However, in children with RE, the overall cost burden of multiple ASMs is often higher than KD, thus future studies looking at cost–benefit ratios of these therapies would be important to gauge economic feasibility, particularly given inconsistent supplies in SSA of ASMS. Finally, admission of participants to a hospital for KD initiation increases the risk of hospital-acquired infections in these otherwise well children. Out-patient initiation is a future consideration, as in established KD centres.

5. Conclusion

Our pilot implementation program demonstrates that KD is a feasible and sustainable alternative option for managing children with DRE in a resource-limited setting. Local expertise, motivated family caregivers and access to specialized education and information via collaboration with an already established KD centre are essential components in the success of the program at the site of implementation. To achieve its greatest benefit in LMIC, improved access to pre-diet exclusion of metabolic disease will also be necessary. Further studies on long-term sustainability and economic feasibility in contrast to polypharmacy will be important.

Ethical statement

Ethical clearance for this pilot trial was obtained from University of Zambia, School of Medicine Bio-Medical Research Ethics Committee in Lusaka, Zambia.

Caregivers were requested to sign consent forms and verbally express their understanding after this training.

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Declaration of competing interest

All the authors confirm that they have no competing interests to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2020.100380.

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