

Dietary therapies for epilepsy in low resource settings: challenges and successes.

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Abstract

The Ketogenic Diet (KD) is a high fat, low carbohydrate and restricted protein diet which has been used for the treatment of drug resistant epilepsy in children. It is considered the treatment of choice for refractory nonsurgical epilepsy in children. However, despite this being an effective and relatively simple treatment, children from developing countries have not been able to benefit as much as their counterparts in more privileged settings. In this article, the challenges faced by pediatric neurologists and parents who wish to use the diet in children with refractory epilepsy are discussed, and also the simple low cost innovations which can be used to overcome these challenges are suggested. The evolution from the use of the classic ketogenic diet to the flexible use of the modified Atkins diet in low resource settings will be discussed.

Keywords: Ketogenic diet; Modified Atkins diet; Low glycemic index treatment; refractory epilepsy

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Introduction

The Ketogenic Diet (KD) is a high fat, low carbohydrate and restricted protein diet which has been used for the treatment of drug resistant epilepsy in children. It has been around for almost 100 years now [1]. In the 1920's and 1930's, it was practically the only treatment available for epilepsy, apart from bromides. Then with the discovery of phenytoin in 1939 and subsequent discovery of other anti-seizure medication (ASM), its use fell into obscurity, as it was perceived to be a difficult and tedious treatment as compared to the simple administration of ASM. However there has been a revival of interest in use of the KD since the 1990's and now it is considered the treatment of choice for refractory epilepsy in children which is not amenable to surgery. The saga of its use over almost a century has been described as "*the ultimate comeback story in the modern era for the treatment of epilepsy*" [1].

The efficacy of the KD for the treatment of refractory epilepsy in children is impressive. Across case series and randomized controlled trials, at least half of the children on the diet have a >50% reduction in seizures and 10-% become seizure free [2]. This efficacy is likely better than most new and emerging ASM but no head-to-head comparisons are available. There are less restrictive variants of the diet such as the modified Atkins diet and the low glycemic index treatment, which have been shown to have similar efficacy as the classic KD [3]. The diet has been shown to have many other positive effects on the brain such as improved cognition and better brain energetic, and is now be-

ing tried in numerous non-epilepsy conditions such as autism spectrum disorder, neurodegenerative conditions, brain tumors, traumatic brain injury and stroke. However, despite this being a very useful and relatively simple treatment, children from developing countries have not been able to benefit as much as children in developed nations. I will discuss the challenges faced in low resource settings regarding the use of the dietary therapies and potential means of overcoming these challenges, with special reference to my experience with the use of the KD and its modifications in India over the last 15 years.

Profile of Childhood Epilepsy in low resource countries

Over fifty million people live with epilepsy worldwide, of whom over 40 million live in low and middle income countries (LMIC) [4]. Around half of these are children [5]. There is a severe shortage of child neurologists in these settings. India, for example, has less than 200 child neurologists (with varying degrees of training ranging from 3 months to 3 years) for its population of 1.33 billion people. There are numerous gaps in availing the treatment of epilepsy in LMIC. These include lack of awareness and knowledge and presence of social stigma; poor access and availability of specialised medical care in terms of child neurologists, pediatric electroencephalography (EEG) services and neuroimaging; and poor access and affordability of anti-convulsant drugs.

The etiological spectrum of refractory childhood epilepsy in low resource settings reflects a high proportion of children with perinatal brain injury and neuro-infections. In a study from the author's center in 2002, it was seen that perinatal brain injury accounted for 48%, and infections for 24% of children with refractory epilepsy [6]. More recent data is not available, but this continues to be the situation as per the author's and other child neurologists' experience (personal communication).

Perinatal brain injuries account for a high proportion of drug resistant epilepsies in children, especially epileptic encephalopathies like West syndrome, which is a common cause of refractory childhood epilepsy [7]. This is because of the high prevalence of home deliveries and suboptimal maternal and newborn care. Neonatal hypoglycemia is emerging as a very important risk factor for refractory epilepsy in India. This is likely because of high prevalence of low birth weight and intrauterine growth retardation, early discharges, and inadequate feeding in the first few days of life [8]. The diagnosis of this entity is increasing because of wider availability of magnetic resonance imaging (MRI) which shows unilateral or bilateral occipital gliosis/cystic encephalomalacia in these children. In a large series of 170 children with epilepsy associated with neonatal hypoglycemic brain injury from our center, 68.2% of the children had refractory epilepsy [8]. West syndrome was the commonest epilepsy syndrome documented. The other important cause of epilepsy in LMIC is infections such as neurocysticercosis, pyogenic meningitis, tubercular meningitis and intracranial tuberculomas and viral encephalitis [5]. Infections are common because of poor sanitation, and non-universal coverage with immunization against *Hemophilus influenzae* and *Streptococcus pneumoniae*.

Treatment gaps in low resource settings

Apart from the shortage of trained personnel and infrastructure needed for the appropriate diagnosis and management of childhood epilepsy as mentioned earlier, there are also problems in drug availability and affordability [9]. In a study mapping the availability, price and affordability of 5 common ASM (phenytoin, carbamazepine, valproic acid, phenobarbital and diazepam) in 46 countries, the authors found that the highest costs of the drugs were found in the lowest income countries [10]. The authors concluded that the availability and affordability of ASM was poor in LMIC and likely acted as a barrier for accessing treatment. The situation is much worse for the newer ASM such as vigabatrin, levetiracetam, topiramate, zonisamide, clobazam and lacosamide. The situation with vigabatrin is especially problematic in India, because of local licensing issues and it is a very expensive and tedious process for parents to import this drug. Rufinamide and Cannabinoids are not available in India.

Epilepsy surgery is a very important treatment option for children with refractory epilepsy and must definitely be explored in all cases. However there is a severe shortage of trained medical personnel and infrastructure for epilepsy surgery in low resource settings. In a scoping review on the availability of epilepsy surgery facilities in LMIC, Watila et al reported that articles on

epilepsy surgery were published from only 22% of the 143 LMIC [11]. The centers are few, and the costs, though much less than the Western countries, still are prohibitively expensive for the poor patients. Also, many children with refractory epilepsy in low resource settings have bilateral gliotic and cystic lesions as a result of perinatal asphyxia, neonatal hypoglycemia and neuroinfections, and may not be good surgical candidates. Vagal nerve stimulation is prohibitively expensive and there is not much data for its use in young children.

Hence the KD seems intuitively a good option for this setting. It has the inherent attractiveness of simplicity and not requiring high tech equipment. Also the KD has been proven to be especially effective in childhood epileptic encephalopathies such as West syndrome, Lennox Gastaut syndrome etc which form a large proportion of children with refractory epilepsy and low resource settings. However there are a lot of challenges with the use of this treatment as well in low resource settings, as discussed below.

Challenges with the use of the KD in India

I began my work on the KD in 2006 under the mentorship of Professor Veena Kalra at the All India Institute of Medical Sciences, New Delhi. A literature review at that time did not reveal any publications of the use of the diet in India. The KD was seen as a fanciful, Western diet and faced considerable scepticism from the adult neurology fraternity. There was limited availability of trained dietitians. Labelled foods were not easily available. Some of the staples of the KD such as heavy fat cream was not available at all.

To add to these problems, the Indian diet is very carbohydrate rich with cereal staples such as rice and chapatis (Indian wheat bread) forming the bulk of the diet. In the usual Indian diet, 65-70% of the calories come from carbohydrates. Hence the transition to the KD where-in only 5-10% of the calories come from carbohydrates is very difficult for Indian patients. Also there is a high population of vegetarianism in India, ranging from 50-90% depending on the region. There also cultural issues of religious myths and taboos, and a high prevalence of joint families where the grandparents also stay with the child. The idea of fasting the child to initiate the diet was not viewed favourably by the families. For patients who lived in rural areas, availability of refrigerator, and continuous power supply was also an issue. In addition, I worked in a Government set up which catered to patients from low and middle socio-economic strata. Bed availability for hospitalization to initiate the diet was scarce. The ability of parents to understand complex instructions about the diet preparation of foods was also limited.

Experience with the use of the KD in India

Keeping these challenges in mind, my colleagues and I conducted our first study on the use of the classic KD in young children with refractory epilepsy [12]. We used a using a non-fasting gradual initiation protocol, as described by Bergqvist et

al. [13]. The diet was formulated using Indian recipes and locally available foods. The outcomes were encouraging; 48% (13 of 27) had >50% reduction in seizures, and four children (15 %) were seizure free at 6 months. This was similar to the previously published Western data. There were however significant adverse effects, which included constipation (74%), weight loss (14.8%), edema due to hypo-albuminemia (7.4%) and renal stones (3.7%) [12].

We realized that the classic 4:1 ratio diet was difficult for the children to tolerate. Also, in-patient initiation was difficult because of limited bed availability. Meanwhile there was data from South Korea where other ratios were evaluated. Seo et al reported similar efficacy and tolerability of 3:1 ratio as compared to a 4:1 ratio diet in children with refractory epilepsy [14]. Also, Nathan et al reported the use of lower ratios (ranging from 2:1 to 4:1) with similar efficacy as reported in Western Literature [15]. These authors also reported the use of carbohydrate wash-out for initiation, out-patient initiation and the use of soya products for vegetarians [15].

A lower ketogenic ratio allows increased carbohydrate intake, leading to improved palatability and closer approximation with the normal Indian diet. We hence conducted a randomized open labeled study comparing a 2.5:1 ratio with the classical 4:1 ratio diet with out-patient initiation [16]. The results showed that 58% in 4:1 group versus 63% in 2.5:1 group had >50% improvement seizures ($p=0.78$). There were no significant differences in the biochemical parameters or adverse effects between the groups.

The modified Atkins Diet

One of the major problems we still faced with the ketogenic diet was the need for parents to understand the complicated instructions of diet preparation and strict weighing of foods. It was difficult for the overworked dieticians to perform these tedious individualized calculations and the parental instructions needed several hours. During this period, studies on the use of the modified Atkins diet (MAD) on childhood epilepsy were published [17]. The MAD is a less restrictive alternative to the traditional ketogenic diet. This diet can be initiated on outpatient basis without fasting and allows unlimited protein and fat [18]. Parents and/or patients are given broad guidelines and asked to choose from the available labeled foods. This diet is therefore considered better for older children, adolescents, and adults.

As the educational level of the parents in our scenario was not high, and there was limited availability of labeled foods in our setting, we “modified” the MAD and adapted it to our setting [19]. We restricted the carbohydrate intake to 10 grams/day. The carbohydrate content of various food items was explained to the parents, and exchange lists were provided. A list of recipes based on common locally available foods, with pre-specified carbohydrate contents (e.g., 2.5 g, 5 g, and so on) was provided. These recipes required weighing of some of the components that contained carbohydrates; the rest of the components could be added as per desire. We found that providing simple instructions with

choice of recipes with pre-calculated carbohydrate contents was feasible for the parents, although it did require some weighing of foods [19]. The counseling time was reduced to 30-45 minutes.

We evaluated this version of the modified Atkins diet in a randomized controlled trial [19]. 102 children aged 2 to 14 years were randomized to receive either the modified Atkins diet or no dietary intervention for a period of 3 months. The mean seizure frequency at 3 months, expressed as a percentage of the baseline, was significantly less in the diet group: 59 (95% CI 44–74.5) versus 95.5 (95% CI 82–109), $p = 0.003$ [19]. The MAD was found to be effective and well tolerated.

We found the MAD useful in children with Lennox Gastaut syndrome (LGS). Out of 25 children with LGS started on the diet, 3 were seizure free and 8 had >50% reduction in seizures at 6 months [20]. Also, we found good efficacy of the MAD in young children with refractory epilepsy and children with infantile spasms who had failed hormonal therapy and/or vigabatrin [21, 22].

Despite our modification of the MAD, we found that parents with low levels of literacy were not able to benefit, as they had to understand instructions and weigh some of the food components. For this group, to further simplify the administration of MAD, this diet, the following modifications were made: the weighing of individual food items with gram scales was replaced with the measuring of individual food items with standardized metric tablespoons and the recipes were depicted by pictorial representation and exchange lists [23]. This diet was then evaluated in 81 children with refractory epilepsy in a randomized-controlled-trial where-in the enrolled children were randomized to receive either the simplified modified Atkins diet or no dietary intervention for a period of 3 months with the ongoing ASM being continued unchanged. The proportion of children with >50% seizure reduction was significantly higher in the diet group as compared to the control group (56.1% vs 7.5%, $p < 0.0001$) [23].

Current scenario of the use of the dietary therapies in India and the way forward

There is a much better awareness of the ketogenic diet amongst doctors and dieticians now, especially with the use of these diets for weight loss in adults. Around 30 centers provide KD to children. There are many publications on the use of dietary therapies in childhood epilepsy from different parts of India [24]. However some challenges still remain. The majority of children with epilepsy are treated by pediatricians and adult neurologists, so there is a need for increasing awareness about the diet in these. There is still a paucity of trained dieticians. Ready to use keto-foods are sparingly available, and only in the big cities. Ketogenic formula is prohibitively expensive.

The minimum requirements for ketogenic services in resource limited regions were published by the International League Against Epilepsy (ILAE) Task force for dietary therapy [25]. The guidelines state that physician supervision (preferably neurologist) is essential for starting the diet. Dieticians are mandatory for classic KD, and optional for alternative diets. The framework

for lab investigations and supplements has been simplified for these settings. This was a much needed step to encourage more child neurologists to start dietary services for their patients.

The Covid pandemic has shown us that training programs and courses can easily be virtual. Interested doctors and dieticians can be trained in the use of these dietary therapies by means of online courses. Telemedicine can be used for patients in remote areas. With increased use and demand for keto products in childhood epilepsy and other neurological conditions, the production and supply of these will increase with competitive cost benefits to the consumers. Policy decisions such as insurance coverage and re-imburement of the ketogenic diet therapies need to be taken at the government level. Parent support groups such as the Charlie foundation (<https://charlifoundation.org/>) and Mathews Friends (<https://www.matthewsfriends.org/>) are needed in our low resource settings to make their voices heard and provide the doctors with a forum for patient advocacy.

Conclusion

Dietary therapies are an important therapeutic option for children with drug refractory epilepsy in low resource settings. They are appropriate for severe epilepsies and epileptic encephalopathies caused by perinatal asphyxia and neonatal hypoglycemic brain injury. The diet can be tried while pending epilepsy surgery work up, or if no epilepsy surgery facilities are available. There are numerous challenges such as lack of trained dieticians, cultural issues, and low literacy levels of the caregivers. However, solutions can always be found if the physician and the family (and dietician if available) are motivated. Simplicity, flexibility and innovation are needed in these settings.

Competing interests

None.

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