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International consensus statement on clinical implementation of the ketogenic diet: Agreement, flexibility, and controversy

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SUMMARY

The ketogenic diet (KD) is an established, effective nonpharmacologic treatment for intractable childhood epilepsy. The KD is provided differently throughout the world, with occasionally significant variations in its administration. There exists a need for more standardized protocols and management recommendations for clinical and research use. In December 2006, the Charlie Foundation commissioned a panel comprised of 26 pediatric epileptologists and dietitians with particular expertise in using the KD. This group was convened to create a consensus statement regarding the clinical management of the KD; the consensus statement has also been endorsed by the Child Neurology Society. Members were asked to write sections based on clinical interests and the full document was subsequently reviewed and approved by the entire group. Recommendations were made regarding evaluation of children before starting the diet, specifically in regards to ideal patient selection, pre-KD counseling and testing, and choice of specific dietary therapy (ketogenic or less restrictive alternative diets). In addition, there was information provided regarding diet implementation (need for fasting and admission), supplementation, follow-up management (frequency of visits as well as diet and laboratory evaluations while receiving the diet), adverse event monitoring, and timing and method of eventual KD discontinuation. This group effort highlights recommendations based on best evidence, including areas of agreement and controversy, unanswered questions, and future research.

KEY WORDS: Ketogenic diet, Consensus statement, Epilepsy.

Once a particular anticonvulsant medication is chosen, the actual provision to children is relatively simple. There are standard guidelines for any particular drug regarding the dose in milligram (per kilogram body weight) the number of doses required per day, liquid or tablet preparations, side effect profile, and therapeutic drug levels. The use of therapeutic diets is not so simple. In fact, many centers provide the ketogenic diet (KD) differently depending on the neurologist and dietitian involved and region of the world (Kossoff & McGrogan, 2005). These differences have likely prevented multicenter prospective research studies, and may have partially contributed to the reluctance of some neurologists to recommend a therapy perceived as so variable in its administration.

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Recognizing these issues, in December 2006 the Charlie Foundation commissioned the creation of a multinational, neurologist- and dietitian-created, consensus statement on the ideal management of children receiving the KD (Kossoff et al., 2008). Unlike American Academy of Neurology sponsored practice parameters, the purpose of this document was to guide the clinical care of children on the KD based not only on research publications but also KD expert opinion. Consensus members were asked to base recommendations on the best quality of evidence available, but not to exclude either retrospective evidence (or single case reports) or their personal opinions.

This author and Beth Zupec-Kania were designated as the coorganizers and first authors of this consensus statement, and 24 additional KD experts were identified based on a combination of published KD research (at least one peer-reviewed publication) and recognized international expertise (Table 1). No more than three individuals from any one hospital were included. Six (26%)

Table 1. Members of the International Ketogenic Diet Consensus Group, listed in alphabetical order

- Per Amark (Sweden)
- Karen Ballaban-Gil (United States)
- A. G. Christina Bergqvist (United States)
- Robyn Blackford (United States)[a]
- Jeffrey Buchhalter (United States)
- Roberto Caraballo (Argentina)
- J. Helen Cross (United Kingdom)
- Maria Dahlin (Sweden)
- Elizabeth J. Donner (Canada)
- Rana Jehle (United States)
- Joerg Klepper (Germany)
- Heung D. Kim (South Korea)
- Eric H. Kossoff (United States)
- Y. M. Christiana Liu (Canada)[a]
- Judy Nation (Australia)[a]
- Douglas Nordli, Jr. (United States)
- Heidi H. Pfeifer (United States)[a]
- Jong M. Rho (United States)
- Carl E. Stafstrom (United States)
- Elizabeth A. Thiele (United States)
- Zahava Turner (United States)[a]
- Pierangelo Veggiotti (Italy)
- Eileen P. G. Vining (United States)
- James W. Wheless (United States)
- Elaine C. Wirrell (Canada, now United States)
- Beth Zupec-Kania (United States)[a]

[a]Nutritionist.

were dietitians, and 11 (42%) were from outside the United States.

Each participant was assigned one topic based on his or her expertise within the use of dietary therapies and each personally contributed two to three paragraphs to the full manuscript. As sections were completed and later reviewed by the full 26-member consensus group for corrections, it became clear that some issues were controversial. A subsequent 15-question survey regarding these particular topics was then emailed to the group to ascertain better the group consensus. The full manuscript has been completed and was subsequently endorsed by the Practice Committee of the Child Neurology Society in March 2008. Overall results are discussed below, highlighting areas of agreement as well as controversy.

Agreement

The consensus group agreed, near universally, on many topics, sometimes even when limited published data was available. Patient selection was one such topic, with 81% of the group agreeing that the KD should be tried after two anticonvulsants have failed, and perhaps first-line for GLUT1 deficiency syndrome (Klepper & Leiendecker, 2007) and pyruvate dehydrogenase deficiency (PDHD) (Wexler et al., 1997). Certain epilepsy syndromes may be particularly well-treated by the KD, including infantile spasms, Dravet syndrome, tuberous sclerosis complex, and myoclonic-astatic epilepsy (Doose syndrome). The pre-KD assessment was also universally agreed upon, including specific laboratory tests required, nutritional assessment, and counseling the family regarding goals and expectations (Farasat et al., 2006).

The majority (88%) routinely admitted children to the hospital to start the KD, but a similar number (77%) believed it could be started on an outpatient basis in select situations (Vaisleib et al., 2004). Once started, all children should receive a multivitamin plus minerals with calcium. Urine ketones should be monitored periodically (as opposed to serum beta-hydroxybutyrate, which was considered optional). Additionally, the group was quite firm on clinic visits to see both a neurologist and dietitian every 3 months, with more frequent visits for infants or children at high nutritional risk. The KD should be tried at least 3 months before discontinuation, and after 2 years the risks should be carefully weighed versus benefits.

Flexibility

There were several topics that the consensus group did not have firm opinions regarding, allowing the individual KD center to decide for themselves. One flexible topic was which specific KD to provide. Based on the available evidence, the consensus concurred that the classic long-chain triglyceride KD diet was similar to the medium chain diet (MCT) , and 96% of the group was also using alternative diets such as the modified Atkins diet (Kossoff et al., 2006) and low glycemic index treatment (Pfeifer & Thiele, 2005). Interestingly, the choice of ratio, calories, and fluids was also left flexible, based on the child's individual nutritional needs rather than for seizure reduction purposes. Additional supplementation with zinc, selenium, Vitamin D, citrates, and laxatives was also left optional. Once on the KD, anticonvulsants can be switched to carbohydrate-free preparations, but the timing of drug withdrawal should be individualized.

Controversy

Despite significant retrospective and prospective evidence for the optional nature of fasting at diet initiation (Kim et al., 2004; Bergqvist et al., 2005), the consensus group had strong but mixed opinions about this topic. Although 58% believed fasting had a role but was optional, 31% stated children should never be fasted and 11% opined that fasting is mandatory at diet initiation. The use of the KD in children who are candidates for surgical resection was also controversial, with 42% not offering the KD to these children (Stainman et al., 2007). A similar percentage would offer only the modified Atkins diet or low glycemic

index treatments to adolescents versus the standard KD. Lastly, the use of carnitine supplementation was mixed, with most centers advocating treatment if blood levels were low, but some members use this supplement only if a child becomes symptomatic (Berry-Kravis et al., 2001).

Conclusion

We believe the creation of this KD consensus statement represents an advance in the clinical management of children receiving dietary therapies. It provides guidance to both KD centers beginning their programs as well as more established hospitals regarding neurological and nutritional recommendations. This manuscript can also serve as a basic template to guide multicenter KD research protocols. Additionally, national epilepsy committees and regulatory agencies can use this document to justify KD treatment, maintenance, and supplementation.

This consensus statement also highlights areas of KD care that are worthy of future study. Many of these topics were discussed in great detail at this international symposium. In several years, we plan to update this consensus statement and again include a survey to determine if practice has changed over time as a result of new research.

Acknowledgment

I confirm that I have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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