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CORRESPONDENCE

To the Editor: The recent paper by Zhao *et al.* (1) claims to identify detrimental effects of the ketogenic diet (KD) on cognitive function in rats. Despite their comprehensive approach to testing cognitive performance, this paper has a serious flaw making it premature to conclude that the KD may pose a potential risk for long-term brain development. Our concern is based on the fact that the KD used by Zhao *et al.* (1) had a fat-to-protein plus carbohydrate ratio of 8.6:1, which is a ratio more than 2-fold higher than found in *any* version of the KD used in children. This extreme ratio appears to have reduced food intake thereby causing much lower weight gain than seen in children given a KD for control of intractable seizures.

The impaired food intake created two related problems. First, ketones cannot meet more than 20–30% of brain energy requirement. By extreme limitation imposed by the 8.6:1 KD on dietary intakes of both carbohydrate and protein (the main gluconeogenic substrate), there was a real risk that the brain was starved of energy substrates. Second, users of the classical KD aim explicitly to meet about 75% of the child's calculated energy demands. This inevitably leads to some restriction in weight gain but most children on the KD remain close to their ideal body weight (2). In contrast, weight gain in the KD-treated animals reported by Zhao *et al.* (1) was 47% and 35% of their two different controls, *i.e.* about *half* the average aimed for clinically. Such brain energy substrate restriction and such severely compromised weight gain both totally confound interpreting outcomes related to cognition. Impaired weight gain, although commonly observed in young rats on the KD, can be avoided if a KD with a clinically relevant fat to protein plus carbohydrate ratio of about 4:1 is used, and if the eventual high fat content of the KD is introduced gradually (3).

The authors acknowledge that weight gain was poor and that protein content of the diet was low (41% of control). However, combining the low protein concentration with lower food intake would make the relative protein intake in the KD group about 40% of 41%, or about 20% of that in controls. Without pair-fed non-KD controls that have the same restricted protein-energy intake and weight gain, altered cognitive outcomes cannot be attributed more to the KD than to the protein-energy restriction. Experiments utilizing a paired approach require a KD and a corresponding non-ketogenic control diet that provide matched protein intakes. One possible formulation for such diets has been reported (4).

Zhao *et al.* (1) demonstrated that absolute brain size was smaller in their two KD groups. However, extrapolating from their figures and compared to the relevant controls, the brain to body weight ratio was 1.53-fold *higher* in the status epilepticus KD group and 2.1-fold *higher* in the non-status epilepticus KD group. These results demonstrate the well-known observation that brain growth is less affected than body growth during severe protein-energy restriction and provide no useful information about the possible risk of the KD *per se* for brain development. Given these serious confounders, the title and abstract are misleading.

Several papers suggesting that "high fat diets" may impair cognitive performance were cited (5–7), but these papers did not use fat intakes anywhere close to that used by Zhao *et al.* (1) or used clinically in children on the KD so the comparisons were inappropriate. Other studies not cited have reported improved long-term neurological prognosis in children on the same formulation of KD used for control of intractable epilepsy (8–10).

Almost all children on the KD for control of intractable seizures have already been unsuccessfully treated with at least three anti-epileptic medications over a period of many months to years. Hence, the delay in starting the KD plus the behavioral and cognitive side effects of several anti-epileptic drugs seriously confound assessing the effects of the KD itself on cognitive development in children.

We have also worked with these experimental challenges in children with epilepsy and in animal models of the KD. Living with seizures is both physically and emotionally debilitating, so verifying whether the KD (a treatment of last resort) affects cognitive development is important but also requires the "most rigorous evidence-based" approach possible (11). There are two relevant issues – is cognitive development at risk on the classical KD used in children and is the reported model appropriately designed? We believe that methodological problems prevent Zhao *et al.* (1) from making an adequate case against the KD on either of these issues.

Stephen C. Cunnane
Research Center on Aging
Sherbrooke University Geriatric Institute
and Professor of Physiology
Université de Sherbrooke
Sherbrooke, QC, Canada J1H 4C4
stephen.cunnane@usherbrooke.ca

Sergei S. Likhodii
Department of Pharmacology
Epilepsy Research Program
University of Toronto
Toronto, ON, Canada M5S1 1A8
sergei.likhodi@utoronto.ca

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Response

To the Editor: We appreciate the interest of Dr. Cunnane and Dr. Likhodii in our recent paper (1). Their letter, which raises a number of excellent points, allows us to make some additional comments about the ketogenic diet and correct one error in our paper.

The first concern by Dr. Cunnane and Dr. Likhodii is that the paper is seriously flawed because of the high fat to protein + carbohydrate ratio of 8.6:1 used in our study. While it is true that this ratio is higher than that typically used in children, we have encountered situations where over-zealous parents have approached this ratio. Moreover, our goal was not to provide an identical diet given to children but rather study the effects of ketosis on cognitive abilities in growing rats. While Dr. Cunnane and Dr. Likhodii would have preferred another diet, our use of this particular diet was not flawed. The diet has been previously used by other investigators (2–5) and, as noted in our paper, the animals tolerated the diet well and gained weight, albeit at a significantly lower rate than that seen in the control animals.

Nevertheless, as we discussed in the paper, we do share the concerns of Dr. Cunnane and Dr. Likhodii about weight gain in relationship to cognitive function. In recent work (6), we have found that caloric restriction during the 1st weeks of life leads to mild cognitive impairment. Interestingly, caloric restriction has been shown to reduce seizure susceptibility (3,5,7). We agree that future studies evaluating the ketogenic diet should use a lower ratio of fat to carbohydrate + protein and avoid the growth failure seen in our animals. The suggestions regarding future study design by Dr. Cunnane and Dr. Likhodii are excellent.

As noted by Dr. Cunnane and Dr. Likhodii, the phenomenon whereby the brain is protected during food deprivation was observed in this study. Nevertheless, brain size did differ among groups. It is not clear why they feel our comments in the text and abstract in regards to brain size are misleading.

Dr. Cunnane and Dr. Likhodii note that the cognitive impairment seen in rats and humans used lower fat concentrations than in our study. We agree and it was for this reason that we have concerns about the cognitive effects of even higher fat concentrations. Dr. Cunnane and Dr. Likhodii will get little argument from us that in some metabolic disorders therapy with the ketogenic diet can be quite beneficial.

As we discussed in the paper, individuals with epilepsy treated successfully with the ketogenic diet with a marked reduction in seizure frequency or intensity often demonstrate dramatic improvements in cognitive function. In our study we found that significantly fewer rats on the ketogenic diet experienced spontaneous seizures than rats on the control diet (Chi-square test = 3.91, $p < 0.05$). We incorrectly stated in the paper that the results were not statistically significant and apologize for this error. The reduction in seizure susceptibility supports prior work from our laboratory that shows a dissociation between the effects of the ketogenic diet on cognition and seizure susceptibility (2).

Finally, we agree that determining the cognitive effects of the ketogenic diet requires a rigorous evidence-based approach. Regrettably, this should have been done in children years ago.

Gregory L. Holmes
Qian Zhao
Section of Neurology
Dartmouth Medical School
Neuroscience Center at Dartmouth
Lebanon, New Hampshire

Carl E. Stafstrom
Department of Neurology
University of Wisconsin School of Medicine
Madison, Wisconsin

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To the Editor: We read with great interest the recent article by Timmons *et al.* (1) on stress/inflammatory responses to exercise in boys and men. While we applaud their efforts to directly compare subjects from these two age groups to research maturational mechanisms of immune responses, one aspect of their data caused us some concern. The authors report that the exercise bout had no effect on circulating interleukin-6 (IL-6) in the boys. This was troubling because of the many cytokines previously reported to be altered acutely by exercise, IL-6 has proved to be the most reproducibly elevated (2). Moreover, we