

Title: The ketogenic diet in brain tumor-related epilepsy

Non-scientific summary

a. Project goals

Dietary therapies for people with epilepsy have been around for a while. The ketogenic diet (a high fat: low carbohydrate: adequate protein diet) has been shown to be beneficial in individuals with refractory epilepsy i.e. epilepsy that does not respond successfully to medication. Primary brain tumor are frequently associated with refractory epilepsy, and in this proposal, our goal is to examine the usefulness of the KETOGENIC DIET in primary brain tumor-related epilepsy. We propose that the KETOGENIC DIET will help not only to decrease seizure frequency, but will also slow down tumor growth.

b. Aims:

- Pre-clinical studies will investigate the role of the ketogenic diet in mice that have brain tumors (these mice have been used extensively by other investigators).
- Clinical studies will examine the role of the ketogenic diet in patients presenting with primary brain tumors with and without epilepsy.

c. Deliverables:

We will be able to tell whether the administration of the ketogenic diet decreases seizure frequency and tumor growth in primary brain tumors.

d. Impact:

The experiments proposed will be performed by members of the Brain Tumor-Related Epilepsy Consortium, making this a collaborative and multi-centered initiative. The Consortium has more than 60 members from 20 institutions who are experts in the fields of epilepsy, neuro-oncology, neuro-surgery, neuropathology, neuro-radiology, neuro-psychology and basic science.

Individuals with brain tumors frequently present with epilepsy – most often than not, seizures are refractory. Decreasing seizures while slowing tumor growth will be especially beneficial in this population. The success of dietary therapies in refractory epilepsy makes us hopeful of its use in tumor-related epilepsy. The results gleaned from this project are applicable to epilepsy without tumors as well.

Scientific summary

Primary brain tumors are frequently associated with epilepsy - seizures can be the presenting sign of a tumor, or they may occur later in the neoplastic process. Current treatment options for brain tumor-related epilepsy (BTRE) are associated with numerous issues (Maschio et al., 2014; Brahimaj et al., 2014; Iuchi et al., 2014), and the exact mechanisms underlying BTRE are not yet understood. However, epilepsy contributes to a substantial decrease in quality of life of individuals with brain tumors. Although brain tumors account for approximately 2% of all cancers in the population (Kohler et al., 2011), the morbidity and mortality associated with brain neoplasms is excessively high including that related to seizures (Ries et al., 2011).

Dietary therapies for epilepsy have been around since ancient times (Wheless, 2008). Currently, the ketogenic diet and some of its alternatives that have better compliance are accepted treatment modalities for refractory epilepsy, and demonstrate effectiveness in

reducing seizures (Pfeifer and Thiele, 2005; Kang et al., 2007; Muzykewicz et al., 2009; Neal et al., 2009). Many theories have been proposed as to why dietary therapy may be effective in seizure treatment, but the underlying mechanism remains unclear. The ketogenic diet produces many metabolic changes with some studies suggesting the importance of GABA (gamma amino butyric acid) levels involved in decreasing excitability in cells. GABA levels both at baseline and during treatment with the diet correlate with a larger decrease in seizure frequency (Freeman, 2006). The ketogenic diet, although very effective for refractory epilepsy (REF) is associated with substantial compliance issues. Alterations of the diet such as the KETOGENIC DIET have been proposed

There is little research regarding the effect of dietary therapy on primary brain neoplasm growth and seizure related events. Multiple rodent studies have demonstrated promising results with the combination of a ketogenic diet and calorie restriction. Cancer cells rely on glucose for their growth and metabolism, and a strong relationship between glucose levels and tumor growth has been observed (Seyfried et al., 2003; Stafford et al. 2010). In addition, an inversely correlative effect between β -hydroxy-butyrate levels and tumor growth has also been observed (Zhou et al., 2007). β -hydroxy-butyrate is one of the ketone bodies that is produced when one is on the ketogenic diet. Preclinical (Abdelwahab et al., 2012; Kim et al., 2014) and clinical (Coppola et al., 2011) studies have suggested the benefit of the KETOGENIC DIET in some epilepsies. Dietary treatment, specifically the KETOGENIC DIET for brain tumors has been suggested (Scheck et al., 2012; Woolf and Scheck, 2015) but never really tried. **Hence, we hypothesize that the ketogenic diet will produce a decrease in seizure frequency and halt tumor growth in primary brain tumors.** This hypothesis will be tested by the following specific aims –

Specific Aim 1 – Examining the effect of ketogenic diet on seizure control and tumor progression in animal models of primary brain tumors.

Specific Aim 2 – Examining the effect of ketogenic diet on seizure control and tumor progression in patients with primary brain tumors. Patients with high grade gliomas (grade III and IV based on WHO classification) will be selected for the study.

Seizure number and severity and tumor growth will be used as endpoints for both aims.

Our research proposal provides **an innovative approach to the prevention and treatment of acquired epilepsy** because the role of dietary therapies in tumors has been suggested, but not really tested. Seizures – whether they are end of life or not – negatively affect quality of life, and refractoriness to anti-epileptic medication is quite common in this population. We propose that the ketogenic diet will be effective in reducing seizures and slowing tumor growth.

The research plan meets the **goals of the Prevention of Acquired Epilepsies Award** because we propose to examine an unexplored, novel target in tumor-related epilepsies: the KETOGENIC DIET. The experiments proposed will be performed by members of the Brain Tumor-related Epilepsy Consortium – a panel of experts in the fields of epilepsy, neuro-oncology, neuro-surgery, neuropathology, neuro-radiology, neuro-psychology and basic science; by pooling resources and expertise, we will be able to expedite research and understanding of the KETOGENIC DIET in tumor-related epilepsies.

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