Information Sheet on the Low Glutamate Diet Pediatric Epilepsy Study

Study Overview

Glutamate has been implicated in epilepsy and seizure occurrence in both animals and humans.[1–3] A major hypothesis for the mechanism of action for seizure occurrence is increased levels of glutamate that result in neuronal excitability and excitotoxicity.[4,5] Excitotoxicity in turn causes oxidative stress and increased neuroinflammation.[6,7] Animal models have demonstrated that elevated glutamate levels can result in seizures.[8–11] Furthermore, monosodium glutamate (MSG), has been used for many years to induce seizures in animal models.[8–16] The association between increased glutamate levels and seizures has also been supported in human studies. Studies using microdialysis have provided evidence of increased glutamate levels during interictal, as well as ictal periods, in people with medically intractable epilepsy in multiple areas of the brain, including the hippocampus and cortex.[17–20] Furthermore, research highlighting the association between seizures and an impaired blood brain barrier (BBB) suggest that this impairment leads to increased glutamate levels in the brain and as a result, excess neuronal firing.[21,22] Since BBB permeability is common in those with epilepsy, dietary glutamate should theoretically be able to affect brain glutamate levels.

The objective of this research is to test a low glutamate diet as a potential adjunct treatment for pediatric epilepsy. The low glutamate diet reduces free glutamate consumption by removing sources of free glutamate (found in food additives and foods with naturally occurring glutamate like soy sauce and aged cheeses), while also maximizing intake of neuroprotective micronutrients, which protect against glutamate induced excitotoxicity, and antioxidants which counter the oxidative stress caused by excitotoxicity.

This is a pilot study that examines the efficacy of the low glutamate diet as a treatment for childhood epilepsy. The primary objective is to assess treatment efficacy based on seizure reduction, while secondary aims are to assess changes in seizure severity, seizure duration, and quality of life.

Background Literature

The low glutamate diet was created in the Nutritional Neuroscience Lab of Dr. Kathleen Holton. As outlined above, glutamate has been strongly implicated in the etiology of seizures, thus, reducing glutamate levels through dietary change could be of profound utility in epilepsy. While healthy individuals are normally protected against high dietary intake of glutamate, any permeability of the blood-brain barrier (BBB) can allow these higher concentrations to access the brain more easily. The BBB has been shown to become permeable from high stress, head injury, hypoxia, and infections.[42-56] Additionally, seizures and epilepsy have been associated with impairment of the BBB.[38] Furthermore, a recent study found that seizure induced BBB disruption in rats resulted in an increased permeability for low and high molecular weight substances.[39] Increased permeability of the BBB would allow dietary glutamate to cross the BBB in much higher amounts, allowing it to potentially affect epileptic activity.

Previous Research on the Low Glutamate Diet

The low glutamate diet has previously been examined in patients with fibromyalgia and irritable bowel syndrome. Fibromyalgia patients have been shown to have higher brain glutamate levels than controls (as have migraine patients).[40–42] Our lab has shown a significant reduction in neurological symptoms among FM patients after 1 month on the low glutamate diet, with a significant return of symptoms upon challenge with MSG relative to placebo in a double-blind

placebo-controlled crossover challenge. In this study, 84% of patients had >30% of their symptoms (avg = 11 symptoms) remit after 1 month on the diet.[43] Symptoms which remitted included diarrhea, abdominal pain, severe fatigue, muscle pain, cognitive dysfunction, problems sleeping, paresthesia, and headache (including migraine), and eight subjects had complete symptom remission.[43] Furthermore, when challenged with monosodium glutamate (MSG), there was a significant return of symptoms as compared to placebo.[43] An improvement in chronic pain symptoms from implementation of the low glutamate diet has also been suggested in global health research on widespread chronic pain in Kenya.[44] The diet was also recently tested in veterans suffering from Gulf War Illness (GWI), which is a chronic pain condition that is also characterized by other neurological symptoms including headache/migraine, widespread chronic pain, fatigue, cognitive dysfunction, anxiety, paresthesia, and sleep issues. Data from this GWI research demonstrated similar profound improvements in neurological symptoms including overall symptom load, chronic pain (including migraine), fatigue, cognitive function (under review at *Brain and Cognition*) and mood disorders (being submitted to *Biological Psychiatry*).[45] There is strong biological plausibility for why there is improvement in these symptoms, as all are known to be associated with abnormal glutamatergic neurotransmission. Of important note, the GWI research has had to restrict access to those who also suffer from seizures due to the challenge portion of the study, where subjects are challenged with MSG versus placebo, which increases risk to subjects with seizures. Since the low glutamate diet has been found to help in other neurological conditions, and glutamate has been implicated in epilepsy and seizure activity, it is highly plausible that the diet could also be effective in epilepsy patients. This study will be the first time the low glutamate diet has been tested in epilepsy. It is important to note that for this epilepsy research, we are removing the challenge with MSG versus placebo we have used previously, to remove any risk of seizure induction.

Research Plan and Methods

The proposed study is a randomized controlled clinical trial to supply evidence of the feasibility, tolerability, and efficacy of a low glutamate diet as a treatment for refractory epilepsy. A wait-listed control group is being used for comparison to subjects' "diet-as-usual," while ethically allowing every person to also have access to the intervention at some point in time.

We are recruiting 40 children with refractory epilepsy. To be included in the study, children must be between the ages of 2 and 21, be experiencing 1 or more seizures per week, have had unsuccessful seizure control with a minimum of 2 anticonvulsant drugs by the time of enrollment, and be willing to keep all medications and Vagus nerve stimulator or Responsive neurostimulation device settings constant during the study period. Additionally, all seizure medications and Vagus nerve stimulator or Responsive neurostimulation device settings will have to have remained constant for 30 days and any previously attempted dietary therapies stopped prior to joining the study. Exclusion criteria includes formula-fed patients, those with inborn errors of metabolism, and non-English speaking households.

Families will be asked to record a seizure diary for a one-month baseline period to establish baseline seizure frequency, duration, and severity. During the last week of the month, families will be asked to complete baseline measures including a seizure assessment form, the Quality of Life in Childhood Epilepsy Questionnaire, the Autism Quotient, the National Institute for Children's Health Quality Vanderbilt Assessment Scale, a Symptom Checklist, a 3-day food diary, Food Frequency Questionnaire (FFQ), and cognitive testing. Once baseline measures are

complete, families will then be randomized to the active intervention group or a one-month waitlisted control group.

Participants randomized to start the diet immediately will receive intensive online nutrition training with Dr. Holton and will be emailed diet materials to support them in following the low-glutamate diet for 1 month. The diet materials include information on food additives to avoid, naturally occurring sources of free glutamate, tricky places these additives are found, shopping lists, recipes (including ways to make healthy food more palatable to children), lists of foods highest in each micronutrient, and a high antioxidant food list. They will have access to Dr. Holton throughout the month to answer questions as they arise. Study measures will again be completed at the end of the one-month period for both active intervention and wait-listed control groups. If waitlisted, controls will then have the opportunity to undergo dietary training, follow the diet for the following month, and then will have all outcomes reassessed.

Medical Oversight

Dr. Kao will serve as medical oversight for the study. Dr. Amy Kao is a pediatric neurologist and epileptologist. She was previously the director of the Dietary Therapies for Epilepsy Clinic at Children's National Medical Center in Washington, D.C. and currently works for the FDA. This research is not related to the FDA.

Contact information

For more information regarding the study please visit clinicaltrials.gov or contact us. For more information on glutamate, dietary glutamate, and epilepsy, please contact Dr. Holton.

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