



High-fat foods, such as cream and butter, are part of the ketogenic diet that can help reduce seizure frequency and intensity in children with epilepsy.

FOOD SCIENCE

Fat chance

For children with epilepsy whose condition is resistant to medication, a high-fat, low-carbohydrate diet may help bring their seizures under control.

BY RACHEL BRAZIL

My nephew, Elijah, had his first seizure when he was 18 months old. Initially, he experienced myoclonic seizures, which are brief muscle contractions that made his muscles stiffen, his arms lift up and his head jerk back. He then developed atonic seizures, in which his muscle lost tone — his muscles would go limp and he would drop to the ground. Elijah was diagnosed with Lennox–Gastaut syndrome, a difficult-to-treat epilepsy that causes multiple daily seizures and severe cognitive impairment.

Over the following 12 months, Elijah's doctors treated him with several antiepilepsy drugs to reduce or stop his seizures. Some of the prescribed medication provided short-lived relief, but there were side effects that included bloating and drowsiness. By the time he was two-and-a-half, Elijah was experiencing more than 50 seizures a day, including generalized tonic–clonic seizures in which the muscles tense and contract and cause convulsions. Falls during his atonic seizures resulted in head injuries, so he started to wear a helmet. His cognitive development stopped. He wasn't speaking or making any attempts to communicate.

At this point, Elijah's neurologist told my sister, Elijah's mother, about the ketogenic diet — low in carbohydrate and high in fat — that may help reduce or stop seizures. My sister was sceptical. A diet that would stop seizures seemed unlikely. Many neurologists were once unwilling to consider the ketogenic diet as a treatment for epilepsy because only anecdotal results were available, but trials conducted in the past decade are prompting a rethink (see 'How fats help epilepsy').

SEIZURE CONTROL

The concept of using food to help treat disease is not new. Ancient Greek texts contain references to dietary therapies for epilepsy, stemming from the observation that starvation stops seizures. Centuries later, in the 1920s and 1930s, doctors commonly prescribed the ketogenic diet for epilepsy in children. During fasting, and in people with diabetes, the liver metabolizes fatty acids into ketone bodies called β -hydroxybutyrate, acetoacetic acid and acetone that are used as an energy source when glucose levels are low. No one knows exactly why, but some evidence suggests that ketone bodies might protect against seizures¹. A low-carbohydrate, high-fat diet creates the state of ketosis — the raised level of ketone

bodies, from which the diet gets its name. The ketogenic diet fell out of favour from 1938, following the availability of a drug called phenytoin that controls the brain's electrical activity and helps to reduce the frequency of seizures. Still, about 30% of epilepsies do not respond to pharmaceuticals, which prompted the search for alternative treatments.

Russell Wilder, a metabolic-disease expert at the Mayo Clinic in Rochester, Minnesota, devised the classic ketogenic diet in 1921. It consists of a weight ratio of 3:1 or 4:1 of fat to a combination of protein and carbohydrate. This means that about 90% of daily calories come from fats, compared with the less than 35% recommended by US Department of Health and Human Services. The ratio is achieved by cutting out grains and adding cream and butter to meals. A ketogenic diet may cause short-term side effects such as constipation and nausea. Longer-term side effects include slowed growth in children and increased risks of bone fractures and kidney stones.

For my sister, the turning point came after Elijah's fourth failed drug. He started the diet in hospital and, under a nutritionist's supervision, was seizure free within six weeks.

Elijah's story is not unique. Some children

who continue to have seizures in spite of treatment with antiepileptic medication experience an improvement on a ketogenic diet. Paediatric neurologist Eric Kossoff of Johns Hopkins Hospital in Baltimore, Maryland, is a leading proponent of the diet and says that of patients who do not respond to an antiepileptic drug, 30% will respond to the next drug they try and 50% will respond to the diet. In the past decade, the short-term success of the diet has been confirmed in four randomized controlled trials², the largest of which enrolled 145 children at London's Great Ormond Street Hospital, and was led by childhood-epilepsy specialist Helen Cross. "About 40% got a more than 50% reduction in seizures," says Cross, and 10% became completely seizure free. Other beneficial effects of a ketogenic diet include statistically significant improvements in attention, social function and sleep patterns³.

DIET DEVELOPMENT

The problem with a ketogenic diet is its unpalatability — such as butter in almost every meal but no bread — which is perhaps why it is used mostly for young children rather than adults. Cross says that when adults try the diet they tend to feel "persistently hungry" because eating a high ratio of fat to carbohydrate and protein leaves many unsatisfied even though they've consumed their required daily calories. Fortunately, there are three alternative diets.

In the 1960s, researchers discovered that medium-chain triglycerides (MCTs) — found in coconut oil — provide greater ketogenic effects than normal dietary fats, which are mainly long-chain triglycerides. The MCT diet, created by the late University of Chicago neurologist Peter Huttenlocher, is restrictive but incorporates more carbohydrates and protein because MCTs are absorbed more easily by the body than long-chain triglycerides. Trials⁴ have found the MCT diet to be as effective as the 4:1 fat-to-carbohydrate ratio in the classic ketogenic diet.

Kossoff, for his part, designed the modified Atkins diet (MAD) in 2003. He says that the idea for the diet arose from observing similar results in people who relaxed the restrictions of the ketogenic diet⁵. In common with the Atkins weight-loss diet, MAD does not involve calorie counting, but limits carbohydrates and encourages fat consumption.

In 2005, the low-glycaemic index treatment (LGIT) came from observations that patients on a ketogenic diet had extremely stable glucose levels⁶. In addition to high fat, the LGIT includes only carbohydrates with a glycaemic index lower than 50, which means that these foods do not tend to increase blood glucose levels. The diet offers more variety — permitted low-glycaemic-index foods include whole grains, green vegetables and berries.

Despite the success of the diets, the mechanism remains largely a mystery. There is little correlation between seizure control and



Elijah enjoying whipped cream with blueberries.

blood ketone body levels. What does change are the metabolic pathways used by some cells, including neurons in the brain. The processes regulating metabolism occur in mitochondria — the organelles inside cells where energy is converted from dietary fuel. This energy conversion process might link diet to reducing epileptic events.

Researchers at two institutions in Boston, Massachusetts, have studied why changing the cell metabolism reduces seizures: cell biologist

HOW FATS HELP EPILEPSY

Epigenetics of eating

A ketogenic diet, which is high in fatty foods such as avocados and low in carbohydrates and sugars, can reduce seizures in children. A paper published last year¹⁰ offers some clues on the way this diet exerts its effect. The researchers looked for genetic changes between rats induced to have epilepsy that were fed a normal diet and those fed a ketogenic diet. They found that the ketogenic diet changes the genetic pathways and could alter the expression of genes responsible for epilepsy. The mechanism is still not clear, but the team noticed that there were differences in the DNA between the two groups of rats. The rats fed a normal diet had a higher amount of methylation — the addition of a CH₃ group — in their DNA compared with the animals fed the ketogenic diet. The team suggests that these changes in methylation are linked to deactivation of the genes.

Nika Danial at the Dana-Farber Cancer Institute and neurobiologist Gary Yellen at Harvard Medical School. Yellen became interested in understanding the diet through his wife, Elizabeth Thiele, a paediatric neurologist at Massachusetts General Hospital and developer of the LGIT diet. Yellen and Danial's work has identified a protein that switches a cell's fuel glucose to ketone bodies and in so doing opens a type of potassium ion channel in neurons that can dampen electrical activity⁷. "Some of the types of cells in the brain where these channels are found are well known as seizure gates that regulate whether a little bit of local excessive electrical activity gets spread to the whole brain and becomes a seizure," Yellen explains.

The success of the MCT diet suggests another pathway to seizure-protection. Neurologist Matthew Walker at University College London and molecular biologist Robin Williams at Royal Holloway, University of London, identified a number of MCTs that provide enhanced seizure control. One example is decanoic acid⁸. Simon Heales, a clinical chemist at University College London, showed that decanoic acid increases mitochondrial numbers in brain cells⁹. The mitochondria produce ATP, which helps transmit signals along the neurons, and its increased production could provide better control of potassium channels related to the seizure gates that Yellen mentions.

There is no agreement on how a ketogenic diet can help control epileptic seizures. It's likely that there isn't a single mechanism involved, and, says Cross, it may work in a different way in different children.

After four years on a ketogenic diet, Elijah has fewer seizures, but he gets hungry and is unable to take part in celebrations that involve food. And he still has severe cognitive impairments and needs assistance with daily tasks such as dressing and feeding.

But he is happy, has an increased attention span and is starting to talk. As Hippocrates, the Ancient Greek father of medicine, said: "Let food be thy medicine and medicine be thy food." ■

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