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New drug holds out promise of normal diet for sufferers of devastating PKU genetic disease

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Imagine being forced to say no to a child crying for more food at supper. Sadly, Margie Fischer doesn't have to imagine it; that was normal life at her family's dinner table for years. Her daughter Maggie, now 20, suffers from phenylketonuria (PKU), a genetic disease that means her body can't tolerate anything more than a low-protein diet.

PKU is described by scientists as an autosomal recessive genetic disease that is characterized by a deficiency in an enzyme called phenylalanine hydroxylase (PAH).

Without PAH, the body cannot metabolize the amino acid phenylalanine. It then builds up in the blood, crosses the blood-brain barrier and causes severe brain damage. Fortunately, PKU can be detected at birth in blood tests, and was one of the first treatable genetic diseases. From infancy, PKU sufferers are restricted to a low-protein diet to avoid the worst complications of the condition. This diet is essential during childhood to prevent damage to the brain while it is still growing; however, it is now also recommended for life to optimize school performance, concentration and the ability to think clearly.

"When Maggie was a little child, we would give her vegetables and we could give her, say, two little sprigs of broccoli," Fischer said. "She would be crying at the dinner table that she wanted more broccoli," Fischer said. "Saying no to a kid who wants more broccoli brought tears

to my eyes. It was so sad."

However, help may now be on the way. A new pharmaceutical being developed by researchers at McGill University and the McGill University Health Centre (MUHC) - along with colleagues at the Scripps Research Institute and BioMarin Pharmaceutical Inc. - is offering PKU sufferers the hope of being able to eat a normal, protein-rich diet. Their preclinical evaluation study was published in December in the *Proceedings of the National Academy of Sciences*.

"The problem is that the PKU dietary modification is extreme," said study first-author Dr. Christineh Sarkissian, a research associate at McGill's Departments of Biology and Human Genetics and the MUHC/Montreal Children's Hospital Research Institute. "It's not a lifestyle choice, it's an obligation, and it's very difficult."

"Maggie needs to eat a special diet which consists largely of drinking an amino acid formula that's very nasty and gritty," Fischer explained. "She can't eat meat, nuts, fish, dairy or grains. And when I say grains, that means no pasta, no bread, no crackers, nothing. So for example, when a typical teen goes out and has a cheeseburger, Maggie can't have the cheese, the meat or the bun. She can have the lettuce and the pickle."

Even individuals who have lived on the restricted PKU diet for years may still suffer health effects into adulthood, Sarkissian explained, especially if they increase their protein intake as they get older.

"The majority of adult PKU patients, depending on how sensitive they are at the blood-brain barrier, will end up suffering from agoraphobia and other reversible conditions that can result from insult to the brain," she said. "The majority of kids who go on to university need to remain on the diet, otherwise they just can't function clearly."

Sarkissian is hopeful that the new injectable treatment she developed with her former supervisor and now colleague, the corresponding author Dr. Charles Scriver - Emeritus Professor of Pediatrics and their academic and industrial collaborators - will make it possible for PKU patients to eat a more normal diet.

"As we go into clinical trials, we'll see how it works in humans," she said. "Certainly in the animal models we showed that the phenylalanine levels came down to normal. The treatment itself is enzyme therapy, so patients will receive an injection once or twice a week instead of, we hope, needing to be on the diet."

"I've got high hopes about this research," said Fischer. "I couldn't be more excited. It would change Maggie's life in two ways: From her point of view, I'm sure the most important thing would be the less restricted diet. She's hungry a lot of the time, she never gets enough food to fill her. She would be excited to eat all the cauliflower she wants, or a whole banana. She's never eaten a whole banana!"

"Aside from just the diet portion," Fischer added, "PKU affects mood and the ability to concentrate, and diet therapy does not work perfectly for everyone. What means the most to me is that the new treatment would allow Maggie to reach her full potential."

Source: McGill University

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