National PKU Alliance

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2010 NPKUA Funded Research Projects

FELLOWSHIP GRANT SUMMARY
"CELL TRANSPLANTATION FOR PHENYLKETONURIA"

Dr. Roberto Gramignoli, Department of Pathology, University of Pittsburgh School of Medicine

Can cell transplantation help individuals with PKU? Dr. Roberto Gramignoli will study this question using "hepatocyte (liver cell) transplantation" (HTX) in the liver, which has been shown to successfully treat other metabolic disorders.

PKU is one of the most common metabolic disorders. Individuals with PKU are deficient in the enzyme, phenylalanine hydroxylase (PAH), needed to metabolize phenylalanine ("phe"). Without PAH, phe accumulates and becomes toxic. Not following a restricted, lifelong diet low in phe can lead to brain damage and other problems for those with PKU

Even with an effective, lifelong diet, there is still an unmet need for alternative treatments for PKU, Gramingnoli states. The importance of his study is that it could change the lives of those who have PKU. Gramignoli notes that it is common for individuals to quit the PKU diet in life because it is unpalatable and expensive. However, going off diet for those with PKU can lead to serious health risks, such as brain damage, memory issues, and seizures.

Studies have indicated that restoring as little as 5 to 10 percent of the PAH deficiency in the liver can correct elevated phe levels, which are what become toxic to those with PKU. PAH is manufactured in the liver and Dr. Gramignoli's study seeks to determine if liver cell transplantation (HTX) can correct the deficiency in a PKU mouse. HTX has been shown to correct metabolic liver disease in many other animals and in patients with metabolic liver disease. If successful in the PKU mice, these studies will generate data to help those affected with PKU.

In his research, Dr. Gramignoli will repopulate the liver of PKU mice by transplanting PAH proficient hepatocytes. These normal liver cells will grow and regenerate in the recipient's liver to restore the livers ability to make PAH. The PAH will then breakdown the phe and correct high phe levels in the blood in those with PKU, allowing them a less restricted diet.

Further, Gramignoli will study changes in brain chemistry after transplantation. Since PKU is associated with phenylalanine hydroxlase (PAH) deficiency, this deficiency leads to changes in brain chemistry, which can cause permanent brain damage. Gramignoli's study proposes that following transplantation, brain chemistry will return to normal as phe levels in the blood normalize. The phe levels therefore would not become toxic.

It is expected that transplanting 5 to 10 percent of donor PAH-proficient cells in the liver will result in decreased phe in the blood in Gramignoli's study. Normalization of phe levels will result in correction of brain imbalances of amino acids and neurotransmitters, and normal PAH activity will result in normal phe levels throughout the body.

RESEARCH GRANT SUMMARY

"MATERNAL PKU: OFFSPRING FOLLOW-UP AND MATERNAL NUTRITIONAL AND PSYCHOLOGICAL STATUS"

Dr. Harvey Levy, Professor of Pediatrics at Harvard Medical School, Senior Physician in Medicine/Genetics at Children's Hospital, Boston

For women affected by PKU, it is essential for the health of their unborn child to maintain a low-phenylalanine ("phe") diet before and during pregnancy. Though the developing fetus may only be a carrier of the PKU gene, the intrauterine environment can have very high levels of phe. The result is that children born to mothers with PKU are at risk for mental retardation, growth restriction and other health risks unless this diet is strictly followed by the mother during pregnancy. Dr. Levy's study seeks to describe the health and well-being of women with maternal PKU and their children by examining and performing psychological assessments, providing a larger study on long-term outcome in maternal PKU. Forty children born to PKU mothers and 25 PKU mothers will be included in the study in the New England region.

PKU, once one of the most frequent causes of mental retardations, is now treatable thanks to the implementation of newborn screening. Those affected by PKU can follow a low-phe diet and avoid health issues. Not adhering to a low-phe diet, however, can result in emotional and neurophysical damage. And for women with PKU carrying a child, damage can occur to the child itself as well. Some women with PKU go off the low-phe diet during and post-pregnancy. The damages to the mother vary – including depression, anxiety, phobias, obsessive-compulsive behavior. For the children, behavioral deficits were also noted.

While correct diet therapy for PKU in pregnant women can prevent birth defects, Dr. Levy says a major clinical question remains: What is the long-term outcome in children from treated PKU pregnancies? An additional question is whether children from untreated PKU in the mother during pregnancy function normally. Dr. Levy's study aims to describe the long-term medical and intellectual outcome in children from maternal PKU pregnancies; to describe the psychological, emotional, and social functioning in children from maternal PKU pregnancies; and to describe the medical and nutritional status and social and emotional functioning of PKU women. Secondary aims include determining which factors of child psychological status may be related to the mother following a low-phe diet during pregnancy to which factors may be environmental; and determining the relationship between previous and current measures of intelligence in children of maternal PKU. The overall goal of the study is to examine the health and well-being of women with maternal PKU and their babies. Both prenatal and postnatal environment factors will also be considered.

Methods for the study of mothers with maternal PKU will include medical and psychological examination, review of nutrition diary and biochemical studies; for the children, a physical, neurological assessment and a psychological assessment will be performed. Data will be analyzed based on characteristics of the mothers and children, including test scores, lab findings, nutrition intake, and background variables.

RESEARCH GRANT SUMMARY

"DOES DIETARY GLYCOMACROPEPTITE IMPROVE BONE DEVELOPMENT IN PKU MICE?"

Dr. Denise Ney, Professor, Department of Nutritional Sciences, University of Wisconsin-Madison

PKU is associated with long term bone loss, resulting in osteoporosis and fractures in early adulthood. This occurrence is becoming more evident in the growing population of adults and adolescents with PKU. The goal of Ney's research is to compare the protein from a GMP diet compared to the traditional diet to improve bone development. The study also will review the relationship between concentrations of phe in the blood and bone development.

Although PKU can be managed by diet without side effects, studies have shown that bone loss is a potential side effect of the traditional PKU diet. A study by Dr. Denise Ney seeks to examine glycomacropeptide (GMP), a whey protein that contains only small amounts of phe, and its relationship to bone development. PKU mice fed GMP show significantly reduced concentrations of phe accumulation in the blood and brain compared with a traditional PKU diet, according to Ney. GMP provides a palatable source of low-phe protein that is an alternative to the traditional diet, thus, GMP is likely to improve compliance with the low-phe diet and improve quality of life for those with PKU, she says.

The GMP diet may ultimately improve bone density and strength in those with PKU because it has a better protein composition that supports collagen during growth. GMP contains higher levels of proline, a major residue in collagen. GMP also has less acid. These factors may improve bone development in PKU individuals compared to the traditional PKU diet.

In her study, PKU mice will be fed low-phe diets containing GMP, traditional PKU diet foods or a control diet. The study will take place for 14 weeks to assess the impact on phe levels in the blood and affects on bone development. The mice will have this diet as their sole source of protein from weaning until early adulthood, which is 14 weeks for mice. Blood samples will be taken from the mice for phe analysis after six weeks of the diet. Statistical analysis and studies, including x-rays, scans and digital photography will follow.

The specific aim of Ney's study is to assess the impact of the GMP diet compared to the traditional diet by looking at bone density, markers of bone turnover and biomechanical performance. The study is best conducted in mice with PKU because of their short lifespan compared to humans with PKU, Ney said. Human bone studies can best follow after research on the mice, she added.

Ney expects that PKU mice fed GMP through young adulthood will show larger bone size, contributing to increased bone mass and strength compared to mice who eat the traditional PKU diet. Such results will support replacing the traditional PKU diet with a better-tasting GMP food product diet. This diet would improve metabolic control and quality of life for those with PKU.