Once-fatal metabolic disorders treatable, says Stanford/Packard researcher

May 31 2007

People with a class of rare genetic disorders that often lead to brain damage, coma and death can be successfully treated with drugs, says a researcher at the Stanford University School of Medicine and Lucile Packard Children's Hospital.

The researchers found in their unprecedented 25-year study that prompt diagnosis coupled with a rapid start of intravenous drug therapy significantly improves the survival rates of people with the condition, called urea cycle disorders. The condition affects proteins in the liver that are necessary to process the by-products of protein metabolism.

"Historically, the prognosis for patients with urea cycle disorders has been universally poor," said Gregory Enns, MD, director of the biochemical genetics program at Packard Children's. "To now be able to talk about the potential for normal outcomes is pretty remarkable."

Enns, who is also associate professor of pediatrics at Stanford's School of Medicine, collaborated with researchers from the Johns Hopkins School of Medicine, the University of Minnesota, Thomas Jefferson University and the Medical College of Wisconsin on the study, which will be published in the May 31 issue of The New England Journal of Medicine. Enns is the lead author of the study, and Hopkins researcher Ada Hamosh, MD, is the senior author.

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diagnosis is often missed or delayed. The study took 25 years to accumulate enough patients to evaluate the drug treatment.

People with urea cycle disorders are unable to convert nitrogen-rich ammonia, a normal by-product of protein metabolism, into urea that is excreted by the body as urine. Mutations in several different proteins can short-circuit the urea cycle, which occurs in the liver, but the result is the same: escalating levels of blood nitrogen cause irreversible brain damage, coma and death.

If a diagnosis is made quickly enough, dialysis can help to cleanse the blood of excess nitrogen during an episode and prevent brain damage.

Traditional treatments included maintaining a very-low protein diet that is still high enough in calories to avoid metabolizing any of the body's protein-rich muscle. Liver transplantation is also an option for some patients.

This study investigated whether drugs that promote alternative pathways to dismantle and excrete nitrogen-containing waste can lower the dangerously high levels of blood ammonia, called hyperammonemia.

The 299 people in the study experienced 1,181 episodes of hyperammonemia during the study period. Those who received the drug therapy had an overall survival rate of 73 percent for newborns and 98 percent for older patients. In contrast, a recent European study of 217 patients who did not receive the therapy reported overall survival rates of only 16 percent for newborns and 72 percent for people with later onset of disease.

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Urea cycle disorders can become apparent at many different stages in life. Newborns with a complete blockage in the cycle begin to show symptoms within hours after birth but are often misdiagnosed. Older children or adults with less-severe mutations can lead normal lives until sickness or a change in diet overtax the body and bring on a life-threatening episode.

Only a fraction of the many possible mutations are picked up by expanded newborn screening, and precious days are lost while test results are processed. The lethargy, vomiting and rapid breathing exhibited by affected newborns are often misinterpreted and mistreated as hospital-acquired infections. "Newborn screening is good at detecting some urea cycle disorders, but we can't diagnose all of them this way," said Enns. "By the time the results come back, these kids are already in the hospital and going into a coma. The sooner you identify them, the better the possible outcome."

Alternative pathway therapy includes a combination of two drugs that work to help the body rid itself of excess nitrogen: sodium phenylacetate and sodium benzoate. Metabolic disease expert Saul Brusilow, MD, at Johns Hopkins' Children's Center, pioneered the drug combination in the 1970s as a possible treatment for urea cycle disorders. Although early reports showed promising results, it took years to gather enough patients to prove the treatment's effectiveness.

Prompt treatment does more than just save lives, however. It also protects patients' brains and gives them a chance at a normal life.

"Traditionally, the cognitive outcome of these disorders has been horrible," said Enns. "There were ethical arguments to be made about even trying to help these kids. The rationale was 'Why treat if you're going to be left with a child who can't do anything"' Now we've shown that we can save these kids."

He added, "Although there are still significant hurdles to overcome - in particular, timely diagnosis - at least we know that normal intelligence is possible. All is not lost when a family gets this diagnosis."

Source: Stanford University Medical Center