

Scientists detect fatal copper disorder at birth

A test developed by NIH scientists could greatly extend the survival of infants with Menkes disease, a rare, otherwise fatal disorder of copper metabolism. The test allows for early diagnosis of the condition, when the chance for successful treatment is greatest. Their work is described in the February 7 *New England Journal of Medicine*.

Untreated, Menkes disease results in irreparable harm to the brain and nervous system. Treatment consists of injections with a copper-containing drug. Children with Menkes disease typically die during the first decade of life. Previously, there was no blood test for early detection of Menkes disease.

“The study represents an important advance in the diagnosis and treatment of a rare but devastating genetic disorder,” said Duane Alexander, M.D., Director of NIH’s National Institute of Child Health and Human Development (NICHD), the lead NIH institute that conducted the study. “The laboratory techniques the researchers used to detect Menkes disease eventually may provide the basis for a newborn screening test to identify children with Menkes at birth, so they have the greatest chance to benefit from treatment.”

The study was a collaboration between researchers in the NICHD, the National Institute of Neurological Disorders and Stroke (NINDS), and the NIH Clinical Center. The NINDS researchers contributed expertise in testing for nervous system chemicals known as catecholamines. Catecholamine levels are determined by a copper-dependent enzyme and for this reason are abnormal in Menkes disease infants.

Menkes disease occurs in about one in 100,000 newborns and is caused by a defect in a gene that regulates copper levels in the body, explained Stephen G. Kaler, M.D., Clinical Director of the NICHD and lead author of the study. This defect, in the gene designated ATP7A, causes abnormally low levels of copper in the brain and liver as well as excessive amounts of copper in the kidneys and intestines. Copper, although only needed in trace amounts, is an essential nutrient that plays a critical role in brain development, he said.

Infants with Menkes disease usually appear normal at birth but start to show developmental delays at 6 to 8 weeks. Affected children may experience seizures and below normal body temperature. Children with Menkes disease also develop distinctive kinky hair, which is steel-colored or colorless and is easily rubbed off the skull.

Dr. Kaler explained that copper is needed for the production of myelin, an insulating material that surrounds certain types of brain and nerve cells. The deposition of myelin around brain and nerve cells is nearly completed by age 2, so the disorder can potentially be treated if copper replacement therapy is started soon after birth. Symptoms of Menkes disease do not usually develop until 2 to 3 months of age, but by that time, the copper deficiency has already caused significant brain damage which treatment seems unable to reverse, Dr. Kaler said.

The defective gene in Menkes disease is located on the X chromosome. Because males have only one X chromosome, they have only one copy of the ATP7A gene and so are severely affected by the disorder. Females have two X chromosomes. If they have a defective ATP7A gene, they are not severely affected, because their remaining X chromosome usually has a functioning ATP7A gene.

In their research, Dr. Kaler and his co-workers evaluated male infants who were considered to be at risk for Menkes disease.

Based on catecholamine levels, the researchers predicted 12 male newborns would develop Menkes disease and administered the copper-containing drug, beginning at a very early age. DNA studies of the ATP7A gene confirmed the diagnosis in each case. The infants were given the copper injections for three years,

receiving two shots daily for the first year and one shot a day during the second and third years. Because long-term exposure to copper can damage the kidneys, the copper injections were stopped after 3 years. The researchers followed the infants throughout childhood to track their survival rates and mental development. Those who received injections soon after birth had a much greater survival rate when compared with a previously documented group of Menkes disease infants who had not received early copper injections.

Of the 12 males in the study, 92 percent were still alive an average of 4.6 years later. Only 13 percent of the males in the earlier group of late-diagnosed patients were alive an average of 1.8 years after diagnosis.

Dr. Kaler said that the study participants did not show any decline in health after stopping the copper replacement.

The boys varied in their response to the copper treatment. Two developed relatively normally, whereas the remainder had varying degrees of developmental impairment. When Dr. Kaler and his coworkers examined the nature of the defect in the boys' ATP7A gene, they found that boys with particular alterations in the gene responded better to the copper injections than did boys with other defects in the gene. They demonstrated that the ATP7A genes of the boys who had the best clinical responses to the copper injections retained some rudimentary capacity to regulate copper.

Dr. Kaler and his colleagues are now working to develop from their research a test that health care providers could use to routinely screen newborn males for Menkes disease.

"I think our findings may be especially meaningful to parents who have suffered due to this condition and lost children to it, Dr. Kaler said. "Menkes disease and other rare disorders of childhood convey a burden to families that is unfair and underappreciated. That a disorder occurs rarely is meaningless if one's child, grandchild, or sibling is affected."

Dr. Kaler added that while additional treatment approaches are still needed for many Menkes patients, the present work signals the beginning of an era when the parents of any infant born with this disease can anticipate better clinical outcomes. He encouraged couples with a family history of Menkes disease to contact the NIH if they have questions about this research study. He can be reached at 301 496-8368.

Source: National Institute of Child Health and Human Development

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