

Kyle Rosen – Pediatric Kidney Disease

At six weeks old, Kyle Rosen developed a 101.5-degree fever. Routine medical tests, including blood work, a urine sample, and sonogram indicated that both of Kyle's kidneys were swollen and that the infant also had a urinary tract infection, which required him to be hospitalized. Kyle's parents, Brett Rosen and Debra Wattenberg, were told by attending physicians that this wasn't too uncommon in infants. They recommended that Kyle take an antibiotic to prevent further kidney infection and then be examined again in six months. Debra, herself a physician, wasn't comfortable waiting that long and had Kyle examined again three months later. This time a sonogram test showed that Kyle had between 20 and 30 stones located in his kidneys. "No one could tell us for sure what was wrong with our son," says Brett. Kyle was diagnosed with everything from overproduction of uric acid to having a possible neurological disease. "Over a period of six months, doctors told my wife and me on two or three separate occasions that our son was going to die." Brett describes the experience as "an emotional roller coaster ride for all of us, including our extended families."

Desperate for answers, Debra and Brett decided to take action of their own. They stayed up late nights researching various diseases over the Internet, as well as talking to several different physicians. They were finally led to a specialist at the Mayo Clinic in Minnesota, who took a biopsy of Kyle's liver and diagnosed the then nine-month old boy with having a rare, or "undefined" form of hyperoxaluria, a genetic disease that results in the formation of kidney stones and that if left untreated could lead to kidney failure. Kyle, now 5 years old, is one of only a very small number of children worldwide diagnosed with this rare form of hyperoxaluria, and the medical community is still uncertain as to the cause or how to successfully treat it. While Kyle's future prognosis is unknown, what is certain is that time is critical for Kyle and other children with hyperoxaluria. Eventually, Kyle's kidneys will shut down and he will need either a kidney, liver or combined liver-kidney transplant, which, though considered valid treatments, come with considerable risk. To help children with this



Debra Wattenberg and Brett Rosen became concerned when their son, Kyle, developed a high fever at six weeks of age. Kyle was eventually diagnosed with a rare form of hyperoxaluria, a metabolic disease that can lead to kidney stones and kidney

failure. Researchers have identified genes thought to contribute to this condition, and hope to develop new therapies in the future. Such diseases exact a cost not only on the patient, but also on the patient's family. The family is hopeful that research will discover more effective approaches for combating this disease.

condition, Kyle's parents serve as active board members of the Oxalosis and Hyperoxaluria Foundation, which works to intensify research efforts.

The NIDDK is seeking to increase research in urinary tract stone disease, including hyperoxaluria. The NIDDK's Division of Kidney, Urologic and Hematologic Diseases has targeted research funds to develop strategies for:

- Correcting the genetic defect in oxalosis and hyperoxaluria;
- Developing new animal models to better study stone diseases; and
- Conducting research on families with a history of these kinds of diseases.

It is hoped that through NIDDK funding and support, new and innovative approaches for addressing the genetic causes and treatment for stone diseases will

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be discovered and disseminated in time to help Kyle and other children who have or may develop the same conditions.

ABOUT OXALOSIS AND HYPEROXALURIA

Hyperoxaluria has several forms, including primary hyperoxaluria type I and type II; unclassified, sometimes referred to as undefined hyperoxaluria; acquired hyperoxaluria; and absorptive or enteric hyperoxaluria. The common factor in all forms of hyperoxaluria is an excessive excretion of oxalate in the urine. Oxalate is normally eliminated by the body. When excess oxalic acid combines with calcium inside the kidneys, the combination results in kidney stones. Oxalosis occurs when the kidneys fail to eliminate calcium oxalate crystals from the body through the urine.

Children with hyperoxaluria suffer from continuous stone formation, which ultimately leads to kidney failure. As this kidney disease progresses, calcium oxalate is deposited in vital organs resulting in disease of the heart, bone, blood vessels, eyes, and finally progressing to end-stage oxalosis, which is potentially fatal.

LIVING WITH THE DISEASE

The severity of hyperoxaluria varies widely, from a complete absence of symptoms and late development of kidney stones to an extremely serious and progressive disease. Most children are diagnosed between the ages of 10 and 20. Kyle, however, was one of the youngest children to be diagnosed with hyperoxaluria of an extremely rare type, and the constant formation of stones in his system has made the first five years of his young life extremely difficult for both him and his family.

At the age of one, for example, physicians removed a urinary stone, or calculus, from Kyle's urinary tract by inserting an endoscope in his penis. Kyle's stones also have been treated with extracorporeal shock wave lithotripsy (ESWL), where shock waves are used to break up the stones so that they can pass through the urinary system. Such treatment requires hospitalization and general anesthesia when treating young children. Despite the immediate relief each procedure brings, it doesn't prevent further stone development.

Each year, Kyle experiences a couple of major stone episodes. "It's excruciating to watch your child continually go through these painful and risky procedures," says Kyle's father, Brett.

A primary treatment for hyperoxaluria is the consumption of large amounts of fluids, which helps keep the kidneys flushed and limits crystal formation. Because of this, Kyle drinks water throughout the day and has been trained to drink a bottle of water and a bottle of apple juice each night. As a result, this otherwise fully active little boy who swims, goes to day camp and pre-school, and functions perfectly well in society still wears diapers at night.

Many patients are also treated with large daily doses of Vitamin B6. Kyle, however, did not respond to Vitamin B6 supplements. He does take magnesium supplements, a diuretic twice daily, and a drug to help retard and prevent stone development. Despite the lack of medical evidence for diet restriction, he also is on an oxalate-reduced diet, which means no chocolate, berries, tomato sauce or ketchup. "When Kyle was three," says Debra, "it was difficult to send him to

HYPEROXALURIA FACTS

- **Hyperoxaluria is a genetic metabolic disease that results in excess oxalate in the urine, which forms kidney stones and may lead to kidney failure. It is most often diagnosed in children between the ages of 10 and 12.**
- **First signs of the disease may be blood in the urine, the painful passage of stones or urinary tract obstruction.**
- **To preserve kidney function, early diagnosis and treatment are essential.**
- **Although millions of Americans suffer kidney stones each year, hyperoxaluria is considered an "orphan disease" (suffered by fewer than 200,000 Americans).**
- **Little is known about the cause of the most common forms of calcium oxalate stone disease, and there are no effective long-term preventive therapies.**

friends' birthday parties and tell him he couldn't eat any pizza, chocolate cake or ice cream, or drink any cola-flavored soda. Now, at age five, Kyle will tell you 'I can't have chocolate or pizza with sauce because I have kidney stones.'"

THE FUTURE

Although urinary tract stone diseases, including all forms of hyperoxaluria, constitute a major health care burden for Americans, little is known about even the cause of the most common forms, and there are no long-term, effective preventive strategies. Recent findings, however, have opened new and exciting avenues for investigation into the cause and progression of kidney stones. Many scientists believe that genetic research is the best hope of finding a permanent cure for the various forms of hyperoxaluria. For example:

- The genes for primary hyperoxaluria types I and II have been identified, which will aid in diagnosing the disease.
- Studies of families with a history of kidney stones indicate that an inherited genetic defect is a likely cause of absorptive hypercalciuria (AH). Researchers have now identified a specific region on chromosome 1 that is associated with a severe form of this disease. It is hoped that further research may permit early diagnoses and possible prevention of kidney stones.

In addition, researchers have identified a new class of bacteria found in human urine and blood, which they believe may be related to levels of calcium in the body. They have also determined that oxalate synthesis is regulated by the metabolic state of the liver. Both of these findings may lead to the development of drugs to combat stone disease. In the meantime, Kyle and his parents hope and pray that a cure for his disease will be found before organ transplantation is necessary. "Finding a cure for calcium oxalate stone disorders will not only help Kyle and patients with primary hyperoxaluria, but the millions of Americans who suffer from kidney stones each year," says Brett.

POSSIBLE VACCINES FOR URINARY TRACT INFECTIONS

Urinary tract infections (UTIs) are one of the most common medical problems in the U.S. A UTI produces symptoms such as painful, frequent urination. Bacterial infections may affect the kidneys, bladder, urethra, or ureters. More than 80 percent of UTIs are caused by the bacterium *Escherichia coli* (*E. coli*). Although antibiotics are frequently used to fight bacterial infections, an increasing number of antibiotic-resistant strains have forced scientists to search for other methods to treat common infections, including UTIs. NIDDK-supported researchers have uncovered new knowledge about how bacteria invade the urinary tract. These discoveries will help scientists develop new treatments for UTIs, such as vaccinations against the disease.

Vaccines work by presenting the body with an inactive form of a microorganism, or component of a microorganism, so that the body can make antibodies designed to attack and destroy it. After vaccination, the body is able to destroy invading microorganisms before they can do damage. Two different NIDDK-supported research groups have attempted to discover proteins that facilitate bacterial infection in order to develop vaccines against them. Both groups have described proteins vital to a bacterium's ability to bind to urinary tract cells.

Prior to invading bladder cells, bacteria attach to the cell surface using a threadlike extension called a pilus. The pilus is made of proteins that have a strong tendency to fold or bind to themselves or nearby proteins. Molecular chaperones are proteins that keep other proteins from binding or folding incorrectly. One research group demonstrated that bacterial pilus assembly requires a molecular chaperone from a family of proteins known as the PapD-like chaperones. Without the chaperone protein, the pilus doesn't form correctly and the bacteria are unable to attach to tissue. Preliminary tests suggest that both monkeys and mice vaccinated against the PapD-like chaperone proteins can resist bladder infections. A second research group identified a sticky protein at the end of the pilus called FimH, which helps the pilus attach to bladder cells. Three out of four monkeys vaccinated with FimH protein were able to fight off bladder infections even after *E. coli* bacteria were injected into their bladders.

This article can be read in its entirety at the NIDDK website!