

The Crigler-Najjar Syndrome Web Pages

Welcome to the Crigler-Najjar Syndrome Web Site

This is a web site devoted to children and adults with the Crigler-Najjar syndrome and their families. It has been created with support and funding from The Rockefeller University. Our mission is to provide information about the Crigler-Najjar syndrome to persons with the disorder, their families and the health professionals who take care of these children. We plan to keep this information updated as new research is published.

We expect to improve this web site considerably based on your feedback. Please contact us with ideas and suggestions for improvement. If there is information or material you would like to see included in this site, please send it to us by mail or email.

We will take great care to ensure that all the information on this web site is accurate. However, before using this information for patient care, you should also confirm from other sources that it is current, accurate and relevant. Please note that the material on this web site is for information only and is not intended to provide specific medical advice to patients. We cannot be held responsible for any inaccuracies in the information on this web site or for differences of opinion between authorities.

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BILIRUBIN BASICS

In order to understand the Crigler-Najjar syndrome well, it is essential to first understand what bilirubin is and how bilirubin is processed in the human body. This section will help you understand what jaundice is, why children with Crigler-Najjar syndrome have jaundice and how the different methods of treatment of this condition work.

What is jaundice?

Jaundice is a yellow discoloration of the skin and the whites of the eyes as a result of having a high bilirubin level in the blood.

What is bilirubin?

Bilirubin (Latin, bilis, bile; ruber, red) is a red bile pigment formed by the breakdown of hemoglobin, which is the red oxygen-carrying substance present in red blood cells circulating in blood. There are also other sources of bilirubin, like myoglobin, a protein present in muscle and enzymes such as cytochromes. Hemoglobin itself consists of two parts, heme and globin. An enzyme called heme oxygenase acts on heme to produce biliverdin, which in turn is converted into bilirubin.

What happens to bilirubin after it is formed?

Bilirubin's ultimate destination is bile, which is made by the liver, but there are several steps it has to go through before it can enter bile. Bilirubin does not dissolve easily in water and therefore it needs a carrier to be transported in the blood. This carrier is albumin. Bilirubin 'sticks' to the albumin in the blood and is carried to the liver. When it reaches the liver cells, bilirubin lets go of albumin and is taken up into the liver cells. Inside the liver cells bilirubin is combined with a substance called glucuronic acid and is changed into conjugated bilirubin. Prior to this it is called unconjugated bilirubin.

Conjugation is a very important step because it makes the bilirubin water soluble, enabling it to get into the bile and be excreted. A crucial enzyme is responsible for the conjugation of bilirubin and this enzyme is called UDP glucuronosyl transferase (or UGT). Bile (with the conjugated bilirubin in it, along with many other substances) flows out from the liver into the bile duct, the gall bladder and finally enters the intestine. Bile has a golden yellow-green color because of the bilirubin in it.

In the intestine, the conjugated bilirubin can follow two paths. It can be excreted in the stool after being changed into urobilinoids. Alternatively, the process of conjugation can get reversed by an enzyme called beta glucuronidase, which converts the conjugated bilirubin back into unconjugated bilirubin. Unlike conjugated bilirubin, unconjugated bilirubin can get reabsorbed from the intestine back into the blood. This process is called entero-hepatic circulation.

Why do persons with Crigler-Najjar syndrome have jaundice?

In persons with Crigler-Najjar syndrome, the crucial enzyme UGT is either missing or is decreased in quantity or activity. Because of this, unconjugated bilirubin cannot get conjugated or is conjugated in small quantities. Therefore it cannot be excreted into the bile and remains in the blood, causing jaundice. If the enzyme is totally missing the person has a severe disorder, called Crigler-Najjar syndrome type I. If the enzyme is decreased in amount or activity, then the disorder is milder and it is called Crigler-Najjar syndrome type II (also known as Arias syndrome). Thus the Crigler-Najjar syndromes are best thought of as deficiencies of the enzyme UDP glucuronosyl transferase. the mildest form of decreased enzyme activity is known as Gilbert Syndrome.

The dangers of having a high bilirubin level

The dangers of high bilirubin levels in the blood have best been studied in newborn babies, who, in the first week of life often have jaundice. In most babies the jaundice is mild and goes away in a few days without any complications. However, there are several conditions that can cause dangerously high levels of jaundice in newborn babies, leading to a form of brain damage called kernicterus. Many of these conditions result from an excessive breakdown of red blood cells (called hemolysis), thereby resulting in the formation of excess amounts of bilirubin, much more than the body can handle.

When there is a dangerously high level of bilirubin in the blood, it can cross into the brain and cause damage to certain parts of the brain, damage which can lead to permanent disabilities and even death.

Types of Crigler-Najjar Syndrome

The Crigler-Najjar syndrome is an inherited disorder of bilirubin metabolism caused by a deficiency or absence of the enzyme bilirubin uridinediphosphoglucuronate glucuronosyl transferase (UGT). There are two types of Crigler-Najjar syndrome. In type I there is no detectable activity of the hepatic enzyme UGT. This results in a severe form of the disease. In type II, also known as Arias syndrome, levels of UGT are <10% of normal. Since some enzyme activity is present, the jaundice is less severe. The following sections describe the etiology, clinical features, diagnosis, management and prognosis of Crigler-Najjar syndrome type I. The articles listed in the bibliography provide more detailed descriptions of the material here.

Crigler-Najjar Syndrome Type 1

Genetics and Molecular Biology

Crigler-Najjar syndrome type I is an autosomal recessive disorder. Bilirubin is conjugated with glucuronic acid by the enzyme bilirubin uridine diphosphate glucuronosyl transferase (B-UGT). UGTs are a group of enzymes that mediate conjugation of many substances with glucuronic acid. They are located on the endoplasmic reticulum and on the nuclear envelope. There are many isoforms, which differ in amino acid sequence, and have different but partially overlapping substrate specificity. They are divided into two major groups, UGT1 and UGT 2, based on the extent of structural homology of cDNAs. UGT1 contains the two isoforms which conjugate bilirubin. UGT2 contains isoforms which conjugate steroids and other substances. The synthesis of these enzymes is controlled by a large gene complex (at least 110 kb) on chromosome 2. This complex consists of four consecutive exons (exons 2 - 5) at the 3' end that encode the identical carboxy-terminal regions of all UGT isoforms expressed from this locus. . Mutations of these exons cause deficiencies of all UGT1 isoforms. Upstream to the common region exons, at the 5' end, is a series of at least seven exons (1A - 1G), each encoding the variable amino-terminal regions of bilirubin UGT1 and UGT2 respectively. Exon 1A encodes the amino-terminal domain of human bilirubin-UGT1, while 1D encodes bilirubin-UGT2. Exons 1F and 1G encode the two phenol UGTs. Because bilirubin UGT1 is the only physiologically significant isoform in bilirubin glucuronidation, mutations in any of its five exons can cause CN type 1 or 2, depending on the severity of its impact on enzyme activity. All patients with CN syndromes have been found to have mutations or deletions in exon 1A, 2, 3, 4 or 5, five exons that encode bilirubin UGT1. The exact nature and extent of the mutations and deletions are variable, with the number of mutations described (currently more than 20) steadily increasing over the years.

Clinical Features

The main clinical problem is jaundice. Typically it starts in the first few days of life and instead of subsiding like physiologic or breast milk jaundice does, persists and increases over the next few days to weeks. There are no other signs or laboratory findings of jaundice from other pathologic causes such as hemolysis or sepsis. In the early stages it may be difficult to differentiate Crigler-Najjar syndrome from jaundice associated with breast-feeding. The jaundice is almost entirely from unconjugated jaundice and there is no elevation of conjugated bilirubin.

The level of jaundice can rise rapidly to high and dangerous levels under certain situations. Such exacerbations ('bilirubin crisis') can occur from hemolysis, infections, fever, trauma (including crush injuries, which can release large amounts of myoglobin), vaccination, fasting, surgery and open liver biopsy. If for some reason treatment is stopped (non-

compliance) the bilirubin can rise rapidly to dangerous levels. Typically this has happened during travel and during adolescence, when teenagers have become non-compliant with therapy.

The constant presence of jaundice can be a significant cosmetic problem to these children and can impair their social interactions with peers, especially during adolescence. They are sometimes mistakenly thought to have hepatitis.

Diagnosis

The possibility of Crigler-Najjar syndrome should be considered when there is a marked elevation of unconjugated bilirubin in the newborn period or infancy without any other evident cause. Thus, evidence of hemolysis, extravascular collections of blood, sepsis, hypothyroidism are all absent. Without treatment, the jaundice shows a continually rising trend.

Laboratory studies show total plasma bilirubin levels ranging from 15 mg/dL to more than 50 mg/dL, with virtually all the pigment being unconjugated bilirubin. The hemoglobin levels, reticulocyte counts, bone marrow morphology and red blood cell survival are all normal. Liver function studies are normal and there are no abnormalities of the extrahepatic biliary system. No bilirubin is found in the urine. Feces are of normal color, despite low levels of fecal urobilinogen. The bile is colorless or pale yellow and contains little or no bilirubin. Of the small amount of bilirubin present in bile, the majority is unconjugated with small amounts of monoconjugates and traces of diconjugates. A liver biopsy shows normal hepatic morphology under the light microscope (except for scattered bile plugs in a few canaliculi) and, on electron microscopy, a non-specific prominence of the smooth endoplasmic reticulum. Definitive diagnosis of Crigler-Najjar syndrome type I requires an assay of the enzyme UGT in hepatic tissue obtained by biopsy. The activity of this enzyme is undetectable. The viability of the sample should be tested before declaring this result.

Management

Phototherapy

The mainstay of treatment for patients with Crigler-Najjar syndrome type I is phototherapy. Phototherapy has been successful in controlling bilirubin levels for years in most of these patients. These children generally need anywhere from 10 to 16 hours of phototherapy a day. This is generally delivered when the child is asleep and most patients with this disorder have specially designed phototherapy beds. Care must be taken to cover the eyes during phototherapy. The intensity of light delivered by the phototherapy unit must be carefully monitored with a radiometer and maintained at a level of at least 4 to 10 microwatts/square cm/nanometer. Higher intensities, for example, up to 40 or 50 microwatts/square cm/nanometer are more effective. If light intensity is decreased, the bulbs have to be changed. Light sources that deliver the appropriate wavelengths of light (425 - 475 nanometers) must be used. The most effective wavelengths are in the blue-green spectrum. 'Special blue' fluorescent tubes are an effective source of light in the blue spectrum. They are labeled F20T12/BB or TL52/20W (Philips) and are different from regular blue tubes (labeled F20T12/B). The greater the surface area of the body that is exposed to light and the greater the intensity of light falling on the skin, the greater is the efficacy of phototherapy. Therefore double surface phototherapy is much more effective than single surface phototherapy. Such double surface phototherapy can be delivered by phototherapy units which deliver light from above the patient as well as from below, generally through transparent material upon which the patient lies. Placing reflecting

surfaces such as mirrors around the child, in order to reflect light onto the skin also increases the efficacy of the phototherapy. A commercially made phototherapy bed for Crigler-Najjar syndrome type I has recently become available.

Unfortunately such prolonged phototherapy severely restricts the child's lifestyle. Traveling and vacations can be problematic (a portable form of the phototherapy bed has been designed). Phototherapy becomes less effective with age and children can become non-compliant with treatment. Side effects of phototherapy include increased insensible water loss, diarrhea and tanning of the skin. The requirement to be almost nude during phototherapy can cause embarrassment to some children and can cause problems with maintenance of body temperature. The protective pads used for the eyes can irritate the eyes. The availability and the cost of lamps has been a problem for some families.

Measures to decrease entero-hepatic circulation

Oral calcium phosphate can potentially be an useful addition to therapy in Crigler-Najjar syndrome type I. A modest effect was found in a placebo-controlled double-blind study which included five patients with Crigler-Najjar syndrome type I. Administered as a mixture of calcium carbonate and calcium phosphate, it caused a decrease in mean bilirubin levels of around 18%. There are anecdotal reports of patients have also been treated with cholestyramine and agar but the efficacy of these therapies has not been well studied.

Other therapies tried

Ursodeoxycholic acid, bilirubin oxidase, antioxidants, calcium infusions, clofibrate, flumecinol, chlorpromazine and urine alkalization have all been reported as potential therapies in Crigler-Najjar syndrome type I. The exact role of these agents in therapy remains to be defined. Phenobarbitone therapy may be tried early in the clinical course when it is uncertain if the patient has Crigler-Najjar syndrome type I or type II but it is ineffective in the treatment of type I disease.

Avoidance of drugs that displace bilirubin

The following drugs can displace bilirubin from albumin, they should be used with caution or not at all, especially when the bilirubin level is high: sulfisoxazole, sulfadiazine, other sulfa drugs, indomethacin, salicylates, furosemide, ampicillin, ceftriaxone, intravenous lipid emulsions. Also, free fatty acids, which can be elevated in sepsis and hypoxia can displace bilirubin.

Tin mesoporphyrin

The rate limiting step in the catabolism of heme to bile pigments is catalyzed by the enzyme heme oxygenase. Tin mesoporphyrin and tin protoporphyrin are synthetic analogues of heme which competitively inhibit heme oxygenase, thereby decreasing the production of bilirubin and lowering plasma bilirubin levels. The unmetabolized heme is excreted into bile. Tin-mesoporphyrin is currently the agent of choice for clinical use because its in vivo potency in inhibition of heme oxygenase activity in animals is substantially greater, and because of its stability and photophysical properties. It is administered by intramuscular injection. Several randomized trials of the efficacy and safety of tin-mesoporphyrin in preventing or treating hyperbilirubinemia have been conducted in full term and preterm newborn infants. These trials show that tin-mesoporphyrin reduces plasma bilirubin levels and either reduces or eliminates the need for phototherapy with minimal side-effects.

Tin mesoporphyrin has been used in two 17year old boys with Crigler-Najjar syndrome type I who had recent neurological deterioration with high bilirubin levels. They were

hospitalized for more than 400 days, underwent 10 hours of phototherapy nightly and consumed constant weight-maintaining diets. They were treated with intermittent plasmapheresis and two periods of tin-mesoporphyrin therapy comprising, in the first study period, 40 doses of 0.5 micromoles/kg and in the second study period, 70 doses of 1 micromoles/kg. Plasma bilirubin levels were decreased in both patients to varying degrees as was the rebound hyperbilirubinemia which occurs after plasmapheresis. The treatments were well tolerated and no progression of the pre-existing neurological impairments occurred during the clinical trials. Both patients experienced episodic mild reversible cutaneous photosensitivity manifested by slight erythema of sun-exposed areas. It was noted that after around 8 to 10 weeks of therapy with tin-mesoporphyrin both patients displayed an 'escape' of the bilirubin effect from the effects of the drug, the mechanism of which is uncertain. These two patients also developed mild iron-deficiency anemia, which responded to iron supplementation.

Tin mesoporphyrin has been used in a 21 month old infant with Crigler-Najjar syndrome type I, again reducing bilirubin levels and reducing the need for phototherapy. Tin-mesoporphyrin has also been used in the management of a 22 year old with Crigler-Najjar syndrome type I who developed a bilirubin crisis following non-compliance with phototherapy. Tin-mesoporphyrin can be an useful pharmacologic adjunct to phototherapy and other treatments to control episodes of acute severe jaundice in Crigler-Najjar syndrome type I.

Liver transplantation

Several patients with CN syndrome type 1 have undergone liver transplantation, which is an effective way to provide the missing enzyme UGT1. Successful transplantation has resulted in very low or normal bilirubin levels and has eliminated the need for phototherapy. However these benefits have to be weighed against the risks and complications of liver transplantation, which is a major surgical procedure. Possible complications of liver transplantation include rejection of the transplanted organ, bleeding, hepatic artery thrombosis, bile duct leaks, and infection. Transplanted patients receive long term immunosuppressant therapy and require periodic blood testing, periodic physician visits and hospitalization for procedures and complications. Two types of liver transplantation have been performed, orthotopic liver transplantation and auxiliary liver transplantation. In orthotopic liver transplantation the patient's liver is removed and a new donor liver is inserted in its place. In auxiliary liver transplantation only part of the patient's liver, usually the left lateral segment, is replaced with a size-matched donor graft. In this procedure, because a portion of the patient's own liver is left in place, the transplanted liver can be surgically removed if there is rejection, allowing the native liver to function as usual, and returning the patient to the pretransplant state with regard to immunosuppression and phototherapy. Also, if other definitive therapy becomes established for Crigler-Najjar syndrome in the future, such as gene therapy, the definitive therapy can be applied to the native liver, allowing the donor liver to be removed and immunosuppression to be stopped. Therefore, it can be treated as a temporizing measure until definitive treatment is discovered. Though auxiliary transplantation has advantages over orthotopic liver transplantation, it is technically more difficult to perform.

Hepatocyte transplantation

One patient, a 10 year old girl with Crigler-Najjar syndrome type 1 has been treated with hepatocyte transplantation. In this procedure the patient's portal vein was catheterized percutaneously and donor hepatocytes were infused over a period of 15 hours with invasive hemodynamic monitoring. She was treated with steroids before and after the procedure and with phenobarbitone after the procedure. After the procedure the patient's

bile showed 33% bilirubin glucuronides (mostly diglucuronide), the UGT activity was 5.5% of normal and eleven months after the procedure her bilirubin level was 14 mg/dL. However she still required 6 to 7 hours of phototherapy every day, which was less than the 10 - 12 hours per day that she had been receiving before the procedure. The long-term results of this procedure are awaited (see www.unmc.edu/news/nejom.htm).

Prognosis

Before the introduction of phototherapy most children with Crigler-Najjar syndrome type I either died in early infancy or developed kernicterus later in life. Phototherapy has changed the natural history of this disease. Currently, with the proper use of phototherapy, bilirubin levels can be controlled and prolonged survival free of neurologic deficits is possible. However patients managed on phototherapy remain at risk of sudden decompensation with a steep rise in bilirubin.

Without treatment the jaundice continues to increase, causing kernicterus and eventually death. This was the fate of many of the patients initially described by Drs. Crigler and Najjar and others. However, with modern management, the level of jaundice can be lowered and kept under control for prolonged periods.

Management of Acute Illness

Preventing Bilirubin Encephalopathy - Management Of A 'Bilirubin Crisis'

With phototherapy most patients have well controlled bilirubin levels. However all patients are at risk for a sudden rise in bilirubin level, which can rapidly cause encephalopathy. Such a rapid rise can have many causes (see above). It is important for parents, physicians and the patients themselves to recognize the risk that such episodes represent. During such an episode the patient may have altered sensorium, inco-ordination, slurring of speech, weakness and can eventually become comatose. Recognition and treatment of such an episode must be quick. Serious delays have occurred in treatment because the physicians managing the patient were either unaware that the patient had Crigler-Najjar syndrome or were unaware of how to manage severe hyperbilirubinemia. Patients with the Crigler-Najjar syndrome type I should consider wearing a Medicalert bracelet. When faced with a newborn infant with hyperbilirubinemia pediatricians, family practitioners and neonatologists, who typically are used to managing infants with relatively benign causes of hyperbilirubinemia, may not consider the possibility that they are dealing with the Crigler-Najjar syndrome type I and may under treat these infants. The American Academy of Pediatrics has issued a practice parameter for the management of hyperbilirubinemia in full term infants (Pediatrics 1994; 94: 558-565). However, it is important to remember that these guidelines apply to healthy full term infants with hyperbilirubinemia and do not apply to patients with Crigler-Najjar syndrome type I.

There are several options for emergency management of severe hyperbilirubinemia:

1. Intense phototherapy should be started.
2. Exchange transfusion. A double volume exchange transfusion is useful in the management of neonates with severe hyperbilirubinemia.
3. Plasmapheresis has been successful in dramatically reducing high bilirubin levels in patients with the Crigler-Najjar syndrome type I. Plasmapheresis may have to be repeated several times.
4. Tin mesoporphyrin can be an useful adjunct to the acute management of patients in a bilirubin crisis.
5. Liver transplantation on a relatively urgent basis should be considered if there is no response to the above measures.

Latest Conference Abstracts

From the Rotterdam Conference, April 29th, 2000 presented by Dr. Maarten Sinaasappel-

Neuropsychological development

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The Crigler Najjar (CN) syndrome is associated with a number of neurological sequelae that tend to evolve abruptly and episodically rather than by slow progression. As yet no clear associations with type of the genetic defect, unconjugated bilirubin levels, medication or neurophysiology have been found. Unfortunately the neurological sequelae have not been documented systematically using similar assessments in a sizeable group of patients in association with these factors. Furthermore, the effect of this disease and its treatment on the quality of life of the patients and their families has not been a subject of investigation. The care for a sizeable group of patients with CN in our hospital provides the opportunity to address both of these issues. Therefore, the aim of our study is to answer the following questions:

1. How is the neurological and neuropsychological function of Dutch CN patients in relation to the type of the defect (Type I or II), their (free) bilirubin levels, medication, and neurophysiology?
2. Is it possible to detect the risk of neurological damage in an early stage of the disease?
3. What are the effects of having the Crigler Najjar syndrome on the quality of life of patients and their families?

All patients with Crigler Najjar who are older than 4 years and are treated in the Sophia Children's Hospital and the University Hospital Rotterdam - Dijkzigt (n = 17) will be enrolled in the study. Patients will complete neuropsychological tests, and patients themselves and their parents or partners will complete questionnaires concerning quality of life of both patients and their families. For all patients extensive standardized and clinical information is available. Patient outcomes will be compared to normative data and neuropsychological outcomes will be related to medical parameters including type of the defect (type I or II), (free) bilirubin levels, medication, and neurophysiology using appropriate parametric and nonparametric measures of association.

Shevell, M.I., Mejnemer, A., & Schiff, D. (1998). Neurologic perspectives of Crigler-Najjar syndrome type I. *Journal of Child Neurology*, 13, 265-269.

Parent to Parent

"This section contains stories and experiences of actual patients with Crigler-Najjar syndrome. We invite other families to submit their own stories to us by email or regular mail, so that we can put them up on this site. To protect your confidentiality, please use first names only or just initials and do not use any identifying characteristics. Pictures of persons with Crigler-Najjar syndrome are also welcome."

Gautham Suresh

2002 Pictures- New!



Amy and Derick with their new colt, Paint.



In June, 2002, three CNS families recently visited Woodward Cave in PA. From left to right: Katherine (non-CNS), Joyce, Dawn, Eric, Amy & Derick in front: Matthew (non-CNS) and Thomas

Waiting for a cure

Gene therapy a hope for beating disease

By Patti Levine-Brown River City News correspondent

The Florida Times-Union

Wednesday, January 3, 2001



Two-year-old Melanie Bryant has to sleep under intense blue lights to help combat the disease Crigler-Najjar Syndrome.

- John Pemberton/staff

Research in the field of gene therapy may be the answer to a prayer for two Jacksonville-area kids who suffer from a rare and deadly inherited liver and metabolic disease.

Melanie Bryant, 2, and Ric DeVere, 16, have a condition known as Crigler-Najjar Syndrome.

Melanie and Ric take numerous medications and sleep under special blue lights. This process, called phototherapy, helps break down bilirubin, which can become toxic to the brain if levels get too high, causing damage much like a stroke.

In those with Crigler's, the bilirubin cannot be excreted from the body, which causes jaundice -- a yellowing of the skin and whites of the eyes.

"Kids have always come up to me and asked why my skin looks yellow," Ric said. "I remember when I was in the third grade I told them I was an alien. I do get aggravated sometimes if someone makes fun of me, but I spend most of my time concentrating on staying healthy and hoping for a cure."

Crigler's does not always strike every child in the family. Melanie's twin brother, Michael, and Ric's younger brother, Hunter, do not have the disease.

Studying families with children who had the disease in the 1940s, physicians John Crigler and Victor Najjar found that parents could be healthy carriers of a recessive gene that causes the disease, and that their children would have a one-in-four chance of inheriting the syndrome.



Steve Bryant carries his daughter Melanie, 2, to her specially designed bed he built with blue lights to combat her liver disease. Said Bryant: "None of us are giving up hope on the possibility of a cure through gene therapy, but we want it to be safe."

-- John Pemberton/staff

The Bryants, who live in Arlington, and the DeVeres, who recently moved from Ponte Vedra Beach to St. Augustine, spent months doing their own research on the disease, which led them to Holmes Morton, a Harvard-educated pediatrician trained in biochemical genetics who worked under Crigler and now runs a special clinic for children with the disease in Strasburg, Pa.

Both Ric and Melanie were tested and shown to be good candidates for an advancement in gene therapy known as chimeraplasty, which is intended to stimulate the patient's own cells to repair the defective gene.

"For years it was very frustrating because we knew Ric was sick, but most doctors did not understand his problems, and we ended up having to take over our son's medical care," said Katie DeVere, Ric's mother. "It was hard to find answers about how to manage his condition because so few doctors knew how to treat this syndrome. Dr. Morton has spent many hours guiding us on what to do for Ric. We think the world of him."

Today, the teenager still suffers from chronic fatigue that often keeps him bedridden, but his mother says it is not as bad as it used to be.

"The fatigue has just about taken away everything Ric used to enjoy doing, including being in school with his friends," Katie DeVere said. "He now has a homebound teacher who is wonderful, but he misses his friends who want him to be able to go along with them. We are proud of how Ric handles his condition, but we all wish he could do the same things others do."

His teacher, Sandy Becker, says Ric is a typical teen who happens to have an ailment that keeps him from doing things he would like to do. "He is a terrific student with a lot of insight," Becker said. "His biggest frustration is that he wants to go to school, but he has limited energy that goes in cycles. It seems that every time I read an article on gene therapy, there has been some new development. I know it is bound to come, but I also know that Ric would love for them to hurry."

Ric, now a 10th-grade homebound student at Nease High School, can only make it to the campus occasionally, but school officials have been understanding. The Bryants say Ric serves as a good role model for Melanie and other kids with the disease who will need his kind of courage and determination to get through their ordeal.

Melanie's parents, Debra and Steve, say they are grateful her condition is presently under control. If gene therapy does not work, children may require liver transplants.

"We have been encouraged by the efforts of doctors who are trying to improve the quality of gene therapy," said Steve Bryant. "None of us are giving up hope on the possibility of a cure through gene therapy, but we want it to be safe."

Both sets of parents realize that medical costs could become catastrophic, especially if a liver transplant is inevitable.

"The children with this disease go through a lot, and we think all of them are heroes," Debra said. "Melanie is taking several pills a day, and these medications are expensive." Ric takes 10 pills four times a day. His monthly medications run in excess of \$500. Still, he continues to have a positive outlook.

"I believe Dr. Morton saved my life, and I want to do the gene therapy," Ric said. "I do not want to have a liver transplant because it doesn't always work, and I don't want to have to take anti-rejection medication for the rest of my life. I get very sad when I think of the boy in England who had a transplant and then got cancer from the anti-rejection medicine." "This is a race against time for Ric, and everyone is doing all they can to keep him healthy," Katie DeVere said. "Our children are the best, and we wouldn't change them in anyway, except to cure them, so we continue to pray for a cure in the new pioneering gene therapy."

Morton has high hopes for success. "If gene therapy works, it will change my life as much as the children it will help," he said. "As a physician, I know we are running a race to keep these children healthy, and my job is to keep them healthy until we can treat the disease. If gene repair works, it will completely change our approach and understanding of how we treat genetic diseases."

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Hello! We are thankful that you are taking the time to learn about Crigler-Najjar Syndrome and some very special children. There are a few Crigler Children in my family. Two are my own.

Derick was born on February 5, 1990. A picture of health, or so we thought! At five days old, he was very jaundiced. His bilirubin level was 22 mg/dl (380 umol). The normal value is 0-1 mg/dl (5-10 umol). He was admitted to the hospital and phototherapy was started. After the fifth day in the hospital, his level was 16. Finally he was able to come home. We had access to a bilirubin light at home and we had to keep him under it 24 hours a day without a diaper. What a mess! Until he was five weeks old, the level never went below 15. It was a very difficult time for us. I cried buckets! Finally, the doctors concluded that he had Crigler-Najjar Syndrome Type 1. We were devastated! We thought that he would never walk or go to school because 8 years prior, a nephew on my husband's side had Crigler that caused severe neurological damage. He died at age three.

God hear our prayers! When Derick was 6 months old, we found Dr. Holmes Morton. Dr. Morton had gone to school with Dr. John Crigler, founder of Crigler-Najjar Syndrome. He has helped us in so many ways and to understand what Crigler-Najjar Syndrome is and how it works seemed so amazing to us.

Our beautiful daughter Amy was born two years later, April 25, 1992. She also has Crigler-Najjar Syndrome type 1. It wasn't easy accepting it the second time around. We got very little sleep. Amy hates her lights. None of the other families we knew about had two children with Crigler. Now we see the benefits of having two children with Crigler-Najjar. They are a team. They have each other to talk to and they stick up for each other when mom makes them take medicine. When children ask Derick why he is yellow, he says, "I have Crigler-Najjar Syndrome and I sleep under a blue light. My sister has it too." When Amy was 2-1/2 years old her bilirubin went up to 39 (670). She had the flu and an ear infection. We kept her under the bili lights 24 hours a day. We ate, played, and slept under the light. She is a miracle! Another boy we know died after a bilirubin of 39.



For years, both Derick and Amy suffered from unexplained stomach pain. Then at age 6 and 4, Dr. Morton discovered that half his Crigler patients had gallstones. Both children had laproscopic surgery. They recovered just in time to travel to NYC to attend the first Crigler-Najjar conference at Rockefeller University.

After Amy's surgery, she still complained of bellyache, chest pains and ate poorly. She was then started on Actigal. What a big difference it made! We will never forget the time I only bought one ice cream cone for both of us because she only ever had 2 licks and I always got the rest. Well, this time she ate the whole cone and I only got 2 licks! We were so thrilled because she was finally happy. The Actigal also reduced their bili levels by 30%.

Derick was having a lot of problems with fatigue. He would lag on behind when biking with his friends. In the evening he would be so tired that he would sit on the steps crying because he could not go up to bed. We had to carry him to bed until I got pain in my back because he was too heavy. When he would wake up in the morning, he would still be tired. We finally took him for a muscle test at Philadelphia Hospital. He now takes creatine 4 times a day and says he feels much better. He can now keep up with his friends and can run up and down the stairs again. Thank God.

My husband makes the bili lights and has sent them all over the U.S. as it is difficult to find lights for these older children. We keep in touch with Crigler families all over the world: Australia, England, Germany, Holland, Italy, Canada, New Mexico, and 8 different states.

We are all looking forward to chimera-plasty. The children already have their pjs and blankets picked out for the first night without lights.

Derick and Amy's story and photos have been in several newspapers and magazines including The New York Times, The Daily Item, National Geographic, Philadelphia Magazine, and Fortune.

April 13, 1999 we were blessed with a baby girl! Katherine Joy. She does not have Crigler-Najjar and isn't even a carrier! We praise the Lord every day!

To all the new Crigler parents, do not give up! God made these children special. They are all beautiful and have a lot of spirit and fight. The future looks bright for them.

Love and prayers,

Katie

Hello from Mifflinburg, PA



Dawn was born on March 16, 1995, on her grandmother's birthday. She was all that we could have wished for; we felt totally blessed!

We noticed that she was getting more and more jaundiced, even though we were keeping her in the sun. At six days old, we got a bilirubin level done through our pediatrician. Her level was 20, so she was admitted to the hospital for phototherapy for 24 hours. Our hearts were broken to see our precious baby girl with no clothes on lying under that awful bright light. That night we prayed that God would make the yellow go away. Memories flashed back of caring for my brain damaged nephew who died at age three from Crigler-Najjar Syndrome. During that time, I was between ten and twelve years old. I remember how I felt when he died. I thought some day I would like a baby like Kevin. He was so sweet, and he was the joy of my life. But all that changes as the years go by, and now my own daughter was under lights! By her seventh day of life, Dawn's level was coming down, but only going back up. So, we had a light made, and tried to accept the fact that she has CNS.

Two and a half years went by and a little boy, Eric, joined the family on October 3, 1997. At this time, the gene test was available, but due to a two week delay, we put him under the lights. Doctor Morton called to tell us what we thought we already knew. He had CNS. He was a content baby and did not mind the light or the sun, so this made it easy for me.

By the age of three, Dawn was quite independent and feisty. She would wake up and lie on the sofa during the night. If I tried to carry her back, she would scream, so I waited until she fell asleep to turn on her light. Nighttime was a busy time. I could tell if they did not get their 8-10 hours under the light. During this time we did not have the Urso which helps to keep their levels down.

Joyce was born on March 25, 1999. She was a chubby, round faced little one that had more or less the nature of our first one. We got our test result five days after she was born. She was already yellow at three days old. We did not want to see it; we were living in denial, yet in our hearts was a great fear we could not push aside. It was an emotional roller coaster. We thought no one ever had three CNS children in a row, so why should we?

I do not have the words to describe the feeling or the days there after what we had to go through, but we believe in a great God and he makes no mistakes. We had to believe that Joyce was no mistake. Looking back, we would not give up any of our children to have an easier life

We look forward to the day they may not have to sleep under the lights, so they too, can lead normal, healthy lives. We are more fortunate that we have always known people with CNS children. I am thankful for the support we have from all of the parents of Crigler children, and last but not least, from Doctor Morton.

Best wishes,
The Martin Family John, Miriam, Dawn, Eric, and Joyce

08/22/00

Fourteen families with a child/children with Crigler-Najjar attended a barbeque at the home of John and Meriam Martin in Mifflinburg, PA on July 22nd. Most of the families live in Pennsylvania, but others traveled from Ohio, Wisconsin, and Kentucky to attend the gathering.

The barbeque provided the parents a chance to talk and share experiences about the disease, and it allowed these very special children a chance to meet and to play with each other.

The Crigler-Najjar children who attended ranged in age from ten months old to sixteen years old. Dr. Holmes Morton and his wife, Caroline, also attended

8/8/00



The Story of Thomas

Thomas was delivered by c-section on September 2, 1999, ten weeks before his due date. I knew he was going to be a small baby, but I never imagined that he would weigh less than two pounds. He was in the NICU for a total of sixty-eight days. He could not come out of his isolette very much because he was jaundiced and needed phototherapy.

As Thomas got older, he gained weight and started drinking from a bottle. Still his jaundice persisted. At about eight weeks old, he had double hernias repaired. He was barely five pounds at this point, but he successfully pulled through.

Doctors kept telling us that they had never seen a baby with chronic jaundice. After consulting medical texts, it was assumed that Thomas must have Crigler-Najjar.

Over three months went by before some test results came back. I searched the Internet for information on this rare topic. I was not sure what the future would hold for a child suffering from this condition. It was not until I was put in contact with families who have children with Crigler-Najjar that I felt hopeful. They reassured me that the children have normal lives except that they must sleep under bililights every night.

Thomas is now crawling and doing things every baby does. He is a beautiful, happy baby. Looking back, the prematurity was simple compared to dealing with a rare disease and living in fear of what may happen.

I used to say "Why did this happen to my baby?" Now my view is that Thomas was one of a few who was chosen to be included in a special group of people. I pray that gene repair will work on these children and that gene therapy can someday cure many diseases.

I am so thankful that the families I have contacted are so willing to share their knowledge with me. One mother I spoke with said it took her thirteen years before she found other families dealing with Crigler-Najjar. I thank God it only took me five months.

Kathleen

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