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Organic Acidemia Association



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Parent Support, Education & Awareness www.oaanews.org

A support group for families living with methylmalonic, propionic, isovaleric, and other organic acidemias

Organic Acidemia Association
13210 35th Avenue N
Plymouth, MN 55441
Phone: 763.559.1797
Fax 866-539-4060
www.oaanews.org

Kathy Stagni,
Executive Director
Propionic Acidemia parent
13210 35th Avenue N
Plymouth, MN 55441
Phone: 763.559.1797
kstagni@oaanews.org

Menta Pitre, Director
MMA Cbl C Parent
207 E. 14th PL
Larose LA 70373
Phone: 985.856.5631
menta@oaanews.org

Cay Welch, Director
Glutaric Acidemia, Type 1 parent
P.O. Box 427
Ridgway, CO 81432
Phone: 970.316.1780
cswelch1@verizon.net

Jana Monaco,
Advocacy Liaison
Isovaleric Acidemia parent
3175 Ironhorse Dr.
Woodbridge, VA, 22192
Phone: 703.497.1216
jana.monaco@verizon.net

OAA: More Than Just a Facebook Group

Family connections have changed dramactically in the past several years – and I wanted to take this opportunity to share the importance of being a 'member' of the Organic Acidemia Association. OAA is a nonprofit organization with the mission statement

> *We are a volunteer non-profit organization whose mission is to empower families and health care professionals with knowledge in organic acidemia metabolic disorders. We support early intervention through expanded newborn screening, solicit contributions and distribute funding that supports research toward improved treatment and eventual cures in the areas of Organic Acid disorders.*

OAA created a Facebook private group several years ago so that families can connect with one another through this social network. Many other 'groups' for each specific OA disorder have been created over the years as well. I want to emphasize that OAA is much more than just a Facebook Support Group. Many of our families use Facebook to find others with the same disorder – which I think is fantastic! I also want to express the importance of "We are all in this together" statement – and the difference between OAA and these Facebook Groups. OAA is a nonprofit, 501(c)(3) organization which was created in 1991. The newsletter has been a source of resource for not only families, but professionals around the world. We host the OAA website and plan and implement a family conference with the FOD Family Support group every other year. Recently a national PKU organization made the decision to stop publishing their newsletter. It's my hope that OAA will continue to publish and share your stories in the OAA newsletter and website. We appreciate your support to continue the important work of supporting families who are dealing with our rare organic acidemias.

Thanks to Jana Monaco for creating another fundraiser for OAA – the "Be Brave" bracelets – they are beautiful! OAA receives $10 for each sale. Here's the link to purchase yours – there are quite a few selections to choose from. Check it out at www.bravelets.com/bravepage/organic-acidemia-metabolic-disorders

BE WELL – BE BRAVE
KATHY STAGNI, EXECUTIVE DIRECTOR

IN THIS ISSUE

Medical Advisors

Dr. Olaf Bodamer FACMG Biochemical Genetics University of Miami
P.O. Box 019132 (M-860)
Miami, FL 33101

Elaina Jurecki, MS, RD
BioMarin Pharmaceutical Inc.
105 Digital Drive
Novato, CA 94949

Keiko Ueda, MPH, RD, LDN
Clinical Dietitian Specialist
Biochemical Diseases (Metabolism) Program
British Columbia Children's Hospital
4480 Oak Street, K3-211
Vancouver, BC V6H 3V4 Canada

Stephen Cederbaum, MD
Mental Retardation Research Ctr./NPI 635
Charles E. Young Dr. South Rm 347
Los Angeles, CA 90095-7332

Stephen G. Kahler, MD
Univ of Arkansas for Medical Sciences
Clinical Genetics Division Slot 512-22
Arkansas Children's Hospital
800 Marshall St.
Little Rock, AR 72202-3591

Charles P. Venditti MD, PhD Genetic Disease Research Branch
National Human Genome Research Institute
National Institutes of Health Bldg 49,
Room 4A56A
Bethesda, MD 20892-4472

Kimberly A. Chapman, MD, PhD, FACMG
Assistant Professor of Pediatrics
Section of Genetics and Metabolism
Children's National Medical Center
111 Michigan Avenue, N.W.
Washington, D.C. 20010

Piero Rinaldo, MD, PhD
Biochemical Genetics Laboratory
Department of Laboratory Medicine
Mayo Clinic
200 First Street SW
Rochester MN 55905

Jerry Vockley, MD, PhD
Professor of Human Genetics & Pediatrics
Chief of Medical Genetics Children's Hospital of Pittsburgh 3705 Fifth Avenue Pittsburgh, PA 15213

Carla Cuthbert, PhD, FACMG, FCCMG
Chief, Newborn Screening and Molecular Biology Branch And the Newborn Screening Quality Assurance Program, Division of Laboratory Sciences, NCEH,Centers for Disease Control and Prevention
4770 Buford Highway, MS-F43
Atlanta, GA. 30341

Mendel Tuchman, MD
Professor of Pediatrics, Biochemistry & Molecular Biology
Children's National Medical Center
111 Michigan Avenue, NW
Washington, DC 20010-2970

Dr. Susan Winter, MD
Valley Children's Hospital
9300 Valley Children's Place C/O Medical Genetics/Metabolism SE11
Madera, CA 93638

MEMORIAL

Fritz: Methylmalonic Acidemia, Mut 0
July 8, 2010 - January 16, 2015

Please join us in saying goodbye to our 4 year old son, Fritz. Fritz fought a life long battle with a rare genetic disorder called methylmalonic acidemia, MMA. With MMA, his body was unable to break down protein. After several respiratory infections and the severe acidosis he faced when sick, he passed away Jan. 16th. Fritz was so full of life, even when he didn't feel good! He loved watching Shrek and listening to music. He attended pre-school and spent 3 days a week going to physical therapy, speech therapy, and occupational therapy. He was always on the go, not much idle time for this kiddo. We are trying to raise awareness of MMA as it is rare and several states still do not have a newborn screening test for some genetic mutations. We would like to offer our support to all the others out there who are fighting a tough battle with their own children. Organic acidemias are on the rise in awareness, but we need more. Thank you for all the kind words and support from all of you!

With Sincere Gratitude,

ANNIE AND PATRICK

Micah : Isovaleric Acidemia | Age 4

We had our first baby- a boy- on a Friday evening in spring of 2010. We were thrilled with how perfect he was, admiring every finger and toe, and gladly took him home after the required two-day stay in the hospital. When he was five days old we woke up to a baby that refused to wake up and eat and had a temperature under 94 degrees farenheit. I remember hurrying out the door knowing we were going to get earth-shattering news. We rushed to the doctor's office and watched the reaction of the medical staff. It was far from reassuring. While we were at the doctor's office Micah's newborn screening came back with an abnormal metabolic reading. I had never heard of newborn screening or metabolic disorders so that didn't mean much to me but our doctor immediately contacted the closest children's hospital and our local ER. We rushed our baby to the ER where they attempted to stabilize his temperature while we waited agonizing hours for him to be transported to the children's hospital.

The children's hospital didn't give us much hope. They did tell us that they thought he had Isovaleric Acidemia and gave us some paperwork explaining the condition. Then we waited. We waited overnight when they intubated him. His body was struggling to expel the extra acid and it wasn't working. We waited the next morning while they put him on medication to stabilize his blood pressure. Then a new resident came on shift and called to tell us that she wanted to transfer him to Cincinnati Children's for further treatment. At this point Micah's heart was beating on its own but they were assisting everything else.

We went back to see Micah one more time before they transported him to CCHMC. I remember standing there crying and looking at my baby. Then I realized that the resident was standing in the corner of the room and she was crying too. Micah was six days old and we were sure we were going to lose him.

When we arrived at CCHMC Micah had been there about thirty minutes. There were medical teams waiting on us to approve procedures to perform dialysis to help clean the acid out of his blood. The risks were significant but they had a plan in case things went wrong. They primed the machine with blood since he was too small for the procedure and started dialysis. It took three tries before his ammonia levels stayed level when they stopped the dialysis. We did a lot more waiting. Waiting for him to come out of his coma; his first cries were precious sounds. Waiting for him to get up to full feeds. And then waiting to be discharged. Two days out from our discharge date Micah started throwing up. The next evening I was standing at the foot of his bed watching the monitors when I noticed some discrepancies as the numbers jumped high and then fell down. Micah was having arrhythmias and they had to call in a specialist to get his IV placed again. He was diagnosed with pyloric stenosis later that week. When they did the pylormyotomy to correct the pyloric stenosis they also placed a g-tube as a precaution.

That g-tube placement was such a blessing to us. Micah had oral issues from his crisis and was able to drink very little of his formula by mouth. For over a year we used the g-tube every time we fed Micah his formula. When he was eighteen months old he started drinking his formula on his own and he loves it now. He's never had any problem eating solid foods. We continued to use the g-tube occasionally whenever he was ill.

Micah has experienced some delays, mostly speech-related, but he's making great progress. His g-tube has been out since October and he participates in typical four-year-old activities. He will turn five in April! Micah receives continued care from the great metabolic staff at Cincinnati Children's Hospital and Medical Center. Along with a reduced protein diet, he continues to consume a formula mix of I-Valex II, carnitine, and glycine on a daily basis.

LISA AND JUSTIN
JOH357@GMAIL.COM

2015 Calendars STILL Available!

Order your calendar from *CafePress.com* and support OAA - we receive a portion of the sale from every purchase. Visit: *www.cafepress.com/organicacidemia*

Maya | Age 5 and Christian | Age 2 : Propionic Acidemia

People always say that you never know true love until you become a mother. I think those people are absolutely correct. I will never forget the moment when my daughter was placed into my arms for the first time. When those beautiful brown eyes peered up at me, my life changed forever. It was Thursday, October 29, 2009 when that little swaddled up bundle of love was wrapped in my arms and overwhelming my heart with joy. My husband Rob and I brought Maya home from the hospital Sunday and received "the call" Monday. "The call" for moms of special needs children may actually be a phone call or maybe it is a face to face with the doctor. Maybe they find out right from the moment of birth, or maybe even before their baby is even born. For us "the call" will forever be engrained in my memory.

someone special
uniquely personalized books
PA Parenting Creates Business

My mom was over helping with the new baby while my husband went to check in on a few things at work. When I answered my phone, the voice on the other side announced they were from the hospital and calling about Maya's newborn prescreening. We already had the all clear, so I was slightly confused. They proceeded to tell me that Maya had an irregular newborn prescreening and may have a metabolic disorder. We were instructed to take her straight to the University of Illinois in Chicago tomorrow morning for further testing. If Maya was lethargic, vomiting, or unresponsive we should bring her straight to the emergency room. That was "the call" that took my breath away. Trying to respond to the person on the phone was nearly impossible. My body fell to the ground while uncontrollable tears poured out. How could this amazingly perfect little baby possibly have anything wrong with her? The next thing I remember is my husband helping me to my feet as I tried to explain the call. I cradled my baby in my arms as my mom, my dad, Rob, and I just stared at her wondering if she was lethargic or sleepy, vomiting or spitting up, and if she was responding properly. My husband called the pediatrician to see if we could stay at the hospital to play it safe.

The next day I watched a genetic team take blood samples, urine samples, and run a variety of tests on my newborn. My husband and I sat with a counselor who asked if I drank, smoked, or took drugs during my pregnancy. He questioned if my husband and I were related, or if there were any complications during my pregnancy. Dumbfounded at the questions that were being asked, I explained what an ideal pregnancy I had with perfect check ups, and how I followed every pregnancy rule that was ever written. As I explained this, I questioned what could I have possibly done wrong? Did I cause this to happen? What is going to happen to my baby?

After hours of tests and waiting, we left with the diagnosis of Propionic Acidemia and were told "not to Google it". The first thing I did when we got home was Google it. I saw words like organic acid disorder, serious health problems, heart abnormalities, seizure, and coma. When the words "possible death" scrolled across my screen, I closed my computer.

Fortunately for us, the only word from the Google list that applies to Maya is "organic acid disorder". Instead of serious health problems, we can say extremely healthy and right on target physically, emotionally, and socially. Instead of heart abnormalities, we can use the words heart of a gymnast. Instead of seizure and coma, our world is full of words like singing, dancing, and laughing. Today Maya is a healthy five year old that attends preschool five days a week, goes to science class and gymnastics through the park district, and loves to boss around her little brother Christian.

Having a sibling for Maya was not the easiest of decisions. Because Propionic Acidemia is a genetic disorder we needed to do the research. After extensive genetic testing and mixed answers on the odds of having another child with Propionic Acidemia, we decided to go with the route of adoption. After a failed adoption, we took our chances and had Christian. Just when I thought my heart could not possibly have room for any more love, I realize just how much love a heart could truly hold. Christian is a handsome, energetic, soon to be two year old. He also has Propionic Acidemia. We were more prepared for the birth of Christian and the possibility of him also having PA. We had a crisis management team in place during the birth and knew within 48 hours our diagnosis.

Both Maya and Christian take specialized formulas and medications. They both receive services through early interventions, and they both have a lot of doctor's appointments. Blood draws are horrendous and doctor's appointments can

be difficult, but none of this defines them. They are loving, caring, energetic bundles of joy with hearts of gold. They respect others, accept everyone, and love unconditionally. Like every other little one, they both have curious and inquisitive personalities.

This inquisitive nature combined with my children's condition is what inspired Someone Special: Uniquely Personalized Books. Kids are curious by nature. They naturally accept everyone's uniqueness and embrace differences, but they also question it. Because Maya's condition revolves around her inability to process proteins, common five year old questions from her peers are as simple, "Why can't Maya eat the pizza? Why does she have to drink that baby formula? Why is she taking medicine; is she sick?" None of these questions are meant to be harmful. They are just curious kids. Children with other disabilities may be faced with different questions such as, "Why is she in a wheelchair? How come he doesn't talk? Why does she need those crutches? How come he acts like that? What are those headphones for?"

To assist with the questions that might be asked about my daughter, I created a personalized picture book for her to show her classmates that she is just like everyone else, but she also has this condition. She likes a lot of the same things as everyone else, but we also need to watch what foods she eats. When I told my best friend and teaching partner Kate Ryan about Maya's book, she instantly knew we could help millions of children the same way I helped Maya. Someone Special: Uniquely Personalized Books was born.

Our plan is to create a personalized children's book for each and every child with a special need. There are books out there about special needs that are educational and kid friendly, and also personalized children's books. However, this unique book will not only personalize the child's name and birth date, but will also include their hobbies, interests, condition and some recommendations that are all personalized by the parent. The parent is also able to choose from a series of illustrations and include a personal photo of their child. The final page of the book is left blank as an open canvas for the parent to include any additional information.

We are still in search of a printer that will be able to print these books at a cost that is affordable to parents. We are hoping to begin printing before the next school year begins in August so that each child can go to school on the first day with their personalized book in hand and a smile on their face.

For updated information on books please visit Someone Special Uniquely Personalized Books Facebook page or their website at *www.someonespecialbooks.com*. Questions or comments can be emailed to *HeatherMcCarthy@SomeoneSpecialBooks.com* or *KateRyan@Someonespecialbooks.com*.

HEATHER AND ROB
OAK LAWN, IL • HMCCARTHY11@HOTMAIL.COM

Lana : Malonic Acidemia | 8 months

Lana was born June 18, 2014, on her due date weighing a healthy 3.4 kg. I had a good pregnancy and a great birth experience. Seemingly healthy and doing well, we were told we could take our baby girl home when she was 2 days old. A nurse would come out to check on us the following day.

It seemed to happen in the blink of an eye. It was our first morning home and suddenly Lana was increasingly agitated. As we were trying to settle her, the nurse arrived. She took one look at her and told us she felt something wasn't right. We didn't understand what she meant, because moments before she seemed OK waking from a nap. Her color was not good and we were told to get her to the hospital immediately. Within the next 5 minutes, Lana changed from a crying baby to a very still one, limp and lifeless; staring into space with a look that made my heart stop. I couldn't breathe and was shaking. I thought is this really happening?

On arrival at the hospital, she was rushed to a bed where a team of doctors crowded her tiny body, hooking her up to monitoring machines and putting in an umbilical and central line. Covered in cords and surrounded by machines, the doctors told us they were testing her for everything possible as they had no clue at this stage, what was wrong. We had no idea of the scale of her sickness until the head nurse told us we that we had a very sick baby and to be prepared that we might lose her. We were shocked and devastated.

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These were the first of many tears as over the next 10 days our beautiful Lana fought for her life. By that afternoon, they had discovered dangerously high levels of acid in her blood, which is a sign that this was a metabolic case. The specialists at the Children's hospital at Westmead were contacted and we were transferred, the following day, to the Grace NICU.

The task was to now figure out which metabolic disorder Lana had. Luckily for us the Professor in charge, Dr Ian Alexander, was on duty and called in his team of pathologists, on a Sunday night, to start the analysis. By the morning, they had discovered that Lana had a very rare metabolic disorder, called Malonic Aciduria. There are only 30 cases ever recorded in the world. Hearing this news was heartbreaking and we broke down in the room filled with Doctors and Nurses who were all treating Lana. I won't forget looking up at the nurses seeing the tears in their eyes and the looks of sadness on everyone's faces. They didn't know much about this disorder and the future was unknown. At this point, Lana was in a very bad way.

Malonic aciduria (MA) is a condition that prevents the body from converting long chain fats into energy. This means she cannot eat food that contains long chain fat and she cannot fast as we contain long chain fat in our bodies that we break down when fasting. If she were to do any of these things the acid levels would build up in her blood again and attack her organs causing acidosis and she would go into a catatonic state, as she did on her 3rd day of life. Other symptoms of MA can be hypotonia, hyperglycemia, seizures, development delay and vomiting, as well as cardiomyopathy, which she was already experiencing. They said MA children can also be small in stature and low in weight.

The next 10 days in NICU were a blur of test after test. Every day there were ups and downs, good news then bad news. We were told that she was the sickest baby here and that her chances of survival were low. We could not believe that we could lose our beautiful baby girl. Sitting by her side hour after hour, day after day, I tried to stay as positive as I could for her. I visualised her at Christmas time, 6 months old, swimming in my sister's pool with our family. I hoped this day would come for us all.

There was a range of problems that Lana was facing due to the acid build up in her blood. Her organs were attacked, in particular her tiny heart, which was now pumping over an inch out of her chest and struggling to work. She was diagnosed with cardiomyopathy and suffered a number of SVTs. There were also concerns she may have brain damage and the acid levels in her blood were still extremely high. We were told this needed to reduce quickly to give her heart a chance to recover. She was placed on a ventilator to give her heart the help it so desperately needed.

After about 7 days, we were receiving more good news than bad. She was on very serious medications and they were being reduced every day and slowly the acid levels were dropping until finally she was in the safe range. Our next hurdle was to slowly take the ventilator off and see if she could pump her heart on her own. This was the hardest. I remember our Doctor saying that they would slowly wean her off the machine as she needed to start pumping her heart herself. I asked "What if she doesn't?" he just looked at us. "Well", he said "Then that's the end"…. It was surreal to hear someone talking so matter-of-factly about whether your child will live or die. We always wanted honesty, to know exactly what was happening to Lana, however difficult it was to digest but to be facing this when this was meant to be one of the happiest times of our lives was soul destroying.

Over that afternoon and evening she was slowly taken off the machines and our little miracle baby, against all odds, started to pump her own heart. This was an incredible turning point. Now she was stable and we were moved out of NICU into HDU down the hall. We used to look into the HDU unit every day on our way to ICU and wish that we were in that room, where the babies were in recovery and were going to be OK. Finally we were moving there. It was a very happy day for us all. From here on we knew our baby girl was going to be OK. The MRI results had come back as clear, with no brain damage visible. They said she would be on heart medications for the rest of her life and that her future, with the metabolic condition, would be uncertain given they didn't know much about it. Even with this news we felt, for the first time, confident that we could now look at our little baby with hope in our eyes and think about a future with her in it. Lana continued to improve and we couldn't have been happier. when after one month in hospital it was time to take her home!

She is now 8 months old and thriving against all odds! She is a healthy weight (adorably chubby) as well as tall and strong. On a recent cardiology visit to the hospital they told us her heart now looks normal and she has already come off one of the heart medications, with plans to take her off the others in the next year or so.

She is the happiest little girl; always ready to give the widest smile to anyone she meets. I am so thankful every day that she is in our lives. Thanks to medicine today, amazing care by the Doctors and Nurses at the Childrens' Hospital, the unwavering support from family and friends and the strong will of our baby girl, Lana. Needless to say, our dream of our bubba in the pool, with her cousins, at Christmas came true. One of the many dreams we have for her to become a reality so far. The future looks bright and happy!

DANIELLE AND STEFAN
SYDNEY, AUSTRALIA • PIPPI1978@HOTMAIL.COM

Understanding Propionic Acidemia Associated Cardiomyopathy

BARUTEAU J 1,2, RAHMAN S 1,2, GRÜNEWALD S 1,2.

1. METABOLIC MEDICINE DEPARTMENT, GREAT ORMOND STREET HOSPITAL, LONDON, UK
2. GENETICS AND GENOMIC MEDICINE, UCL INSTITUTE OF CHILD HEALTH, LONDON, UK

Introduction

Propionic acidemia (PA) is one of the commonest inherited organic acidemias and is caused by a deficiency of the enzyme propionylCoA carboxylase, which breaks down propionic acid, an intermediate chemical from the breakdown of four amino acids (Methionine, Threonine, Valine, Isoleucine), odd-chain fatty acids and the side chain of cholesterol.

In individuals with propionylCoA carboxylase deficiency, propionate (or propionic acid) accumulates and causes toxic effects in various organs, but especially the brain, heart, muscle, liver, pancreas….

Many affected patients develop symptoms in the newborn period with severe ketoacidosis and hyperammonaemic coma, but some individuals have milder late-onset forms of the disease, with recurrent episodes of ketoacidosis triggered by stresses such as infections or prolonged fasting.

Treatment usually requires a protein-restricted diet, avoiding prolonged fasting, supplementation with carnitine and sometimes bicarbonate and biotin. Liver transplantation is a very invasive treatment and does not completely cure the disease, but can significantly improve the symptoms since the transplanted liver can remove large amounts of propionate.

Long-term complications, such as pancreatitis or cardiomyopathy that can progress to heart failure, can occur even in well-treated and stable patients. The underlying mechanisms are still not well understood and are discussed in this article.

Our report

Our metabolic team has recently reported two brothers affected with late-onset PA1. The oldest brother was diagnosed at 18 months of age after several episodes of ketoacidosis. He received conventional medical treatment, and did not have any further episodes of decompensation. He had grown well and his overall development was normal.
At the age of 15 years, an echocardiography was performed as part of a regular review. An asymptomatic mild dilatation of the left ventricle was observed.

At 17 years, after a 6-week period of increasing lethargy, he was diagnosed with severe heart failure caused by a dilated cardiomyopathy and a mild metabolic decompensation.

The metabolic decompensation was quickly resolved in 72 hours by exclusion of dietary protein and treatment with ammonia scavengers.

The patient needed intensive care support in view of the severity of the heart failure. He was on hemofiltration extrarenal removal of propionate for one week. An artificial heart (also called ventricular assist implantation system or Berlin Heart EXCOR) was implanted one week after admission, and was used for the following 2 months. This mechanical device allows bypass of the heart and blood oxygenation via an artificial membrane.

Meanwhile blood results showed low levels of vitamin D (25 OH-cholecalciferol), and coenzyme Q10 (CoQ10). A cardiac biopsy confirmed low CoQ10 levels and a mildly low activity of one enzyme complex (complex IV) of the mitochondrial respiratory chain. He was supplemented with carnitine, ketone bodies and vitamin D (cholecalciferol).

A combination of medications, sometimes referred to as a "mitochondrial cocktail" was provided, aiming to optimise energy production. This cocktail included vitamins (vitamin B2 or riboflavin, vitamin H or thiamine), and CoQ10.

The heart dysfunction improved gradually and the patient was discharged home 3 months after admission, continuing on the "mitochondrial cocktail". Six months after admission, he was able to play football for 90 minutes without feeling any fatigue.

Despite being on an appropriate diet and regular medication including CoQ10 supplementation, the patient was readmitted nine months later with a deterioration of his cardiomyopathy. He was too unwell to be considered for transplantation and unfortunately died from late-stage heart failure in the following days.

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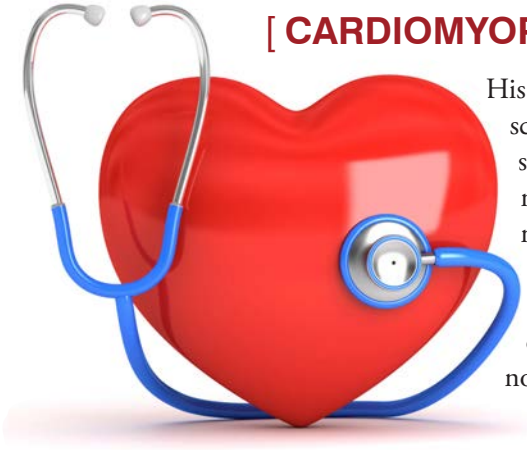

His 15 year old brother was screened after the diagnosis of his brother and has never experienced any metabolic decompensations. He was diagnosed with a mild dilated cardiomyopathy with a low normal level of CoQ10 in white blood cells and has been started on CoQ10 supplementation.

Cardiomyopathy, a well-recognised complication of PA

PA associated cardiomyopathy was first reported more than 20 years ago and is now a well-described complication, with more than 26 cases published. It can affect either early-onset or late-onset cases with a similar severity. The mortality rate is high (9/24; 37.5%). On echocardiography the heart usually appears dilated (14/15 cases).

Acutely treatment usually requires artificial hemodynamic support (systems of partial or full hemodynamic assistance such as the artificial heart) or cardiac transplantation, and hemofiltration to remove toxic metabolites. Secondarily a liver transplant is often performed to prevent a recurrence of the cardiomyopathy in either the native heart, or even the transplanted heart if a cardiac transplantation was performed in the initial acute phase.

The pathophysiology of cardiomyopathy in PA is poorly understood. Several explanations have been proposed: secondary depletion of carnitine consumed in removing excess propionate, which is excreted as propionylcarnitine; direct toxicity of propionate on the energy production system; oxidative stress; and antioxidant depletion.

Secondary mitochondrial dysfunction in PA

Mitochondria are the cellular factories for energy production in the presence of oxygen, a process that is also known as aerobic respiration. The mitochondrial oxidative phosphorylation (OXPHOS) system is coupled with the synthesis of a molecule called ATP (adenosine triphosphate) required by the vast majority of biochemical reactions requiring energy in the body. The OXPHOS system is composed of 5 multiprotein complexes and each complex has a specific role in the transfer of electrons and synthesis of ATP. When mitochondria are not working properly, as in mitochondrial diseases, organ failure can occur due to lack of energy.

The functionality of the OXPHOS system can be assessed by specific enzyme assays, which measure the activity of each complex in tissues obtained from biopsies (muscle, liver, heart, skin fibroblasts).

Several arguments support secondary mitochondrial dysfunction as one of the main pathophysiological explanations for PA associated cardiomyopathy:

- We reported in the cardiac biopsy of our patient abnormal enlarged mitochondria, which can also be seen in patients with primary mitochondrial dysfunction. Furthermore, the activity of complex IV of the mitochondrial respiratory chain was abnormal in our patient.
- Previous publications in PA have reported low levels of different OXPHOS complexes in heart, muscle or liver suggesting a possible link between PA and mitochondrial impairment.
- PropionylCoA carboxylase is an enzyme located in the inner mitochondrial membrane closely to the respiratory chain. Propionate is known to inhibit the mitochondrial Krebs cycle, which is an essential biochemical pathway coupled to the respiratory chain.
- Mitochondria control the production of reactive oxygen species 2. ROS have important functions such as cell signalling but excess can damage DNA, modify structural components of the cells such as proteins and lipids and lead to cell death. ROS are known to be increased in situation of mitochondrial dysfunction. This causes an “oxidative stress” and can deplete the reserves of antioxidants such as CoQ10. The low levels of CoQ10 in white blood cells and in the cardiac biopsy of our patient are paramount observations that confirm the theory of mitochondrial dysfunction as a key player in PA associated cardiomyopathy.

What are the therapeutics that can help mitochondria?

Few treatments have proven their efficacy until now and CoQ10 is one of the potential helpful agents.

Coenzyme Q10, a therapeutic adjuvant in PA?

CoQ10, also called ubiquinone, is a vitamin-like compound and is part of the respiratory chain. CoQ10 deficiency can result either from reduced biosynthesis or increased consumption. Reduced synthesis can be observed in inherited genetic diseases affecting the mitochondria responsible for a primary CoQ10 deficiency.

In secondary mitochondrial dysfunction, an imbalance between oxidative molecules (the ROS mentioned earlier) and antioxidants such as CoQ10 occurs, and the resulting oxidative stress is thought to deplete the mitochondrial stocks of CoQ10.

As the intracellular synthesis of CoQ10 is the major

source of supply, deficiency can arise in situations of chronic mitochondrial impairment.

Pharmaceutical supplementation may help to restore intracellular levels of CoQ10 and has been used in various metabolic condition including mitochondrial disorders.

We believe that secondary mitochondrial dysfunction is the predominant mechanism responsible for PA associated cardiomyopathy and likely also other complications seen in this disorder. Thus, it is reasonable to assess CoQ10 levels in white blood cells and tissues if biopsies are performed in patients with PA. If levels are low, supplementation with high doses of CoQ10 may be indicated. It is challenging to predict intracellular levels of CoQ10 in an organ from white blood cell levels; this could potentially explain why, in our report, a relapse of the cardiomyopathy would have happened despite appropriate CoQ10 supplementation.

Will this supplementation be sufficient enough to prevent long-term complications or even reverse complications when they have occurred? These questions are difficult to answer. A randomised placebo controlled double-blind clinical trial of CoQ10 supplementation in PA would help to answer this question.

This discussion would be identical for other organic acidemias such as methylmalonic acidemia (MMA), which involves the next enzyme in the metabolic pathway. Low CoQ10 levels have also been reported in patients with MMA, as well as suspicion of secondary mitochondrial dysfunction.

Conclusion

- Cardiomyopathy is a severe and not uncommon complication of PA, which can happen even in well-treated and "metabolically stable" patients.
- We describe a case report, which brings evidence for secondary mitochondrial dysfunction being the main pathophysiological mechanism for this complication in PA. Low CoQ10 in white blood cells and in the myocardium are thought to be a consequence of mitochondrial dysfunction and oxidative stress, which is confirmed by abnormal activities of the mitochondrial respiratory chain.
- In our report, clinical proof of efficacy of CoQ10 supplementation is not absolute. Indeed during the first episode of severe heart failure, various treatments were added at the same time and it is retrospectively challenging to acknowledge the merit of each one. Moreover the relapse despite appropriate supplementation is arguably doubtful about this efficacy. More studies will be required to prove this association significantly. However some important conclusions can be drawn: the CoQ10 status of a patient should be assessed and supplementation should be considered to potentially prevent and treat PA complications associated with secondary mitochondrial dysfunction.
- This observation in PA is likely also valid for MMA.

1 Baruteau, J. et al. Successful reversal of propionic acidemia associated cardiomyopathy: evidence for low myocardial coenzyme Q10 status and secondary mitochondrial dysfunction as an underlying pathophysiological mechanism. Mitochondrion 17, 150-156, doi:10.1016/j.mito.2014.07.001 (2014).

DR JULIEN BARUTEAU
RESEARCH TRAINING FELLOW | GENE TRANSFER TECHNOLOGY GROUP
UCL INSTITUTE FOR WOMEN'S HEALTH
86-96 CHENIES MEWS, LONDON WC1E 6HX, UNITED KINGDOM

MEMORIAL

Emilio: Propionic Acidemia

August 21, 1997 - November 12, 2014

Always Remembered Never Forgotten

He passed away November 12, 2014
His death took us by surprise
Never again will we hear or see him smile
Or look into his Loving eyes

His body is cold
Yet his hands are warm
His eyes are closed
And we realize he's gone

We are both in the room
And we feel so alone
Knowing that our boy
will not be coming home

The day the machines were turned off
Was the hardest decision we had to make
But now his life has ended
All we can do is grieve
We know your in good hands

The three hour drive home
God only knows how we made it!
Living with unbearable pain
Even when the sun shines
All we see is rain

The tears echo in our hearts
There is a gaping hole in our heart
'Cause it seems he was too young
And everyone agrees
Cause Emilo was only 17

Pray you are running and enjoying
a new life in the Heavens
with your brother and family
wait for us, as we will be holding both
of you again One day.

SON OF JIMMY & NORA

Exploring the Effects of Organic Acidemia on Pregnancy:

A New NIH Study Designed to Help Moms-To-Be and the Medical Community

Donna Raval M.D. Combined Medical Genetics and Maternal-Fetal Medicine Fellow, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892 and Charles P. Venditti M.D., Ph.D. National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892

Women with inherited metabolic disorders, including those with previously life-limiting conditions such as methylmalonic acidemia (MMA) and other organic acidemias, are reaching childbearing age more often due to advances in early diagnosis and improved pediatric care. For the affected women, their families, and care providers, there is very little information in the literature to guide the counseling and treatment for patients during pregnancy.

To begin to examine this very important problem, we evaluated pregnancies in which the mother had MMA and was enrolled at the NIH as well as those women who were previously published in the literature. We identified a total of 17 pregnancies were identified in women with isolated MMA and 13 completed pregnancies [3 cases with cblA (4 pregnancies), 4 cases of mut- (1 cobalamin responsive, 3 non-responsive), 5 cases with unknown type of MMA]. 17% of the pregnancies resulted in a first trimester miscarriage, while 38.5% of the completed pregnancies resulted in preterm deliveries. The women had a cesarean delivery 53.8% of the time. Fetal distress or nonreassuring fetal status was the indication for 57% cesarean deliveries. Only one patient was reported to have metabolic crisis as well as episodes of mildly elevated ammonia. Malformations or adverse outcomes in the children were not observed. Although there have been a small number of pregnancies identified in women with MMA, the cumulative results suggest that more than expected proportion of the pregnancies were complicated by cesarean delivery and an increased risk of prematurity. We have recently published a paper that details our study [Raval DB, Merideth M, Sloan JL, Braverman NE, Conway RL, Manoli I, and Venditti CP. (2015) Methylmalonic acidemia (MMA) in pregnancy: a case series and literature review. J Inherit Metab Dis. 2015 Jan 8. [Epub ahead of print] PubMed PMID: 25567501].

To us, the findings from our study clearly indicate the need for a pregnancy registry to help clarify perinatal complications and define management approaches needed to ensure optimal maternal and fetal outcomes in this growing patient population, in MMA and other women with organic acidemias. The most information for the effects of an underlying inborn error of metabolism in pregnancy derives from the study of phenylketonuria (PKU). From the knowledge gained through the collection of information from multiple cases of pregnancy affected by PKU, important management issues were identified. For example, children born to mothers with PKU who took an unrestricted diet were substantially more likely to have intellectual disability, microcephaly, and low birth weights than women who maintained a phenylalanine restricted diet. The excess phenylalanine poses long-term health risks to the developing fetus and now a vigilant metabolic approach is recognized as mandatory in women with PKU desiring pregnancy.

Compared to PKU, most or all other intermediary metabolic disorders have been understudied. For example, there are nine published cases of methylmalonic acidemia (MMA) and one case of cobalamin C deficiency in pregnancy. For other inborn errors of metabolism there is even less published or described. The paucity of publication of pregnancy in IEMs other than PKU may be due to the lack of organized research to address pregnancy management in metabolic disorders.

To help gather information regarding pregnancy for patients with all organic acidemias, we have taken the first steps to establish a pregnancy registry of women with inborn errors of metabolism other than PKU. We now have a dedicated research study to help answer these questions (For more information go to *http://clinicalstudies.info.nih.gov/cgi/detail.cgi?A_2015-HG-0049.html* or *ClinicalTrials.gov* Identifier: NCT02322177). If you, your family member or medical team would like to participate, study information will be provided and a permission form next signed (pending interest of course) to allow us to collect medical records with your metabolic and obstetrical issues as well as fetal/neonatal outcomes of your offspring. Our study will also investigate reproductive issues including infertility and use of artificial reproductive technologies. It should be emphasized that all record collection and review is only done after you approve and is confidential.

A pregnancy registry of this type will allow physicians and patients to report varying management and outcomes, both positive and negative, with the broader goal of optimizing maternal and fetal outcomes in pregnancies complicated by organic acidemias. Our registry data would also serve to disseminate management experience for all providers, recognizing that individual centers may be assisted by the cumulative experience as they manage patients with organic acidemias during pregnancy.

If you, your family or your health care providers would like more information about this research study, please contact Dr Donna Raval (*donna.raval@nih.gov*) or Dr Charles Venditti (*Venditti@mail.nih.gov*). We would be delighted to talk to you or others about the study.

Kamryn : Malonic Acidemia | Age 4

On August 15, 2011, I was getting ready for my scheduled C-Section for my third child. Kamryn Marie Able was born with no complications. She was a rather large baby, weighing in at 9lbs 1 oz, but of course, beautiful! The day we were getting ready to go home, her pediatrician heard a heart murmur. After performing an echo cardiogram, it was discovered that she had some holes in her heart, but they were small and nothing to be concerned about. Of course my husband and I were quite nervous about her heart, but we were able to go home and all was right with the world.

The day after we arrived home, we got the dreaded phone call. Kamryn's new born screening had come back abnormal. To be quite honest, I wasn't even sure what the newborn screening was at the time! Our pediatrician called and explained what was going on and requested that we re-test her the following day. I was a wreck. My husband and parents tried to console me, but looking back I just knew something wasn't right. She acted like a perfectly normal baby, but I just had that gut feeling something was wrong. Her re-test was performed on a Friday and by Monday we had the results. This is when the worrying truly began.

The next day, we were at Lurie's Children's Hospital in Chicago, IL talking with genetic counselors, geneticists, and nutritionists. All of them told us that her levels had come down on the second test, but they were still elevated. They said we had a better shot at hitting the lottery than her having Malonic Aciduria. I guess I should have bought a ticket! The following week, her lab work confirmed that there was an issue and we needed to come up and discuss her formula and overall lifestyle. We were in complete shock. We had two other healthy children at home and had no idea what to do. So I immediately jumped on the internet and started "Googling" the disease…NOT a good idea!

Every piece of information I saw stated that we were going to be lucky if she made it through infancy and if she did, she would more than likely have severe mental development issues, cardiomyopathy, muscle development issues, and the list went on. We were devastated to say the least.

We immediately started Kamryn on her new formula, Lipistart. We were told by our doctors that we should perform frequent feedings and to watch for any symptoms, such as hypoglycemia. I finally asked the doctors what specialist I needed to fly her to see in order to ensure she was getting the appropriate care. They just stared at me. They explained that there were no specialists and Kamryn was one of 30 cases ever reported. We left that hospital visit feeling very confused, distraught, and just all around depressed. For the next following weeks, we began to realize that Kamryn was behaving like all our other children and really, she was doing quite well.

Luckily, Kamryn has been developing like a normal child! She began walking at 7 months old and has continued to amaze her doctors. We have not had any episodes that have required a hospital stay at this time, and we count our blessings every day. Kamryn is now 3 ½ years old and a complete joy to be around. She is really starting to understand what she can and cannot eat and will ask if it has "fat" in it! She amazes us every day with her positive attitude and determination. Kamryn does not let anything stand in her way!

After Kamryn was born, we felt like we needed to do something for kids suffering from rare diseases. We knew that we didn't want other parents to have to feel the same way we did when leaving that hospital visit with her diagnosis. So, we set up "The Hope Fund". We had our fist fundraising event in March of 2012 and raised over $10,000. This is when we started the Malonic Aciduria Research Grant in conjunction with NORD, The National Organization of Rare Diseases. Last year we raised over $20,000 and are very close to meeting our research grant goal! This year we are in the process of preparing for our St. Patty's Day Bash which will be held on March 21, 2015 in Kankakee, IL. Tickets are $50/per couple, which includes dinner and live band! We will have a silent and live auction as well. The ticket also enters the couple in for three cash prize drawings. First prize will be $1000, second prize will be $500, and third prize will be $250! For more information about our event or tickets, contact *fundthehope@yahoo.com*.

We are very hopeful that we will meet our research goal this year. Finally, we can get some new research about this disease and possibly what the future entails for these children

KASIE AND GRAHAM
CHEBANSE, ILLINOIS
KASELEIGH00@YAHOO.COM

Organic Acidemia Association

13210 35th Avenue North
Plymouth, MN 55441

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