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

Organic Acidemia Association



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Parent Support, Education & Awareness www.oaanews.org

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Hard to believe its fall again – this year has just flown by! Happy to report that we had another successful family conference in July (see group photo). We were excited that we were able to host the conference in Arlington, VA this year. There are many to thank for assisting in organizing a conference of this magnitude. First of all – our many sponsors! If we did not have sponsors – we could not have hosted this conference! Of course my husband and Melissa were a huge help with assisting in set-up, etc. prior to the conference and onsite. My FOD partner, Deb Lee Gould was so instrumental in organizing all of the registrations and all-in-all a huge help! Eileen Shank and Jana Monaco assisted in locating and securing the hotel accommodations. Karen Dalton helped me create all of our name tags! Raymonde DeGrace created another wonderful ending ceremony video – check it out at https://animoto.com/play/zThdJp6zpkjvOiYGe8aQQQ. Presentations from the conference can be found on our website - www.oaanews.org/2014ConferencePresentations.htm.

Not certain where or if we'll have another conference in two years – this is dependent on finding a major sponsor. In the meantime, there are many opportunities for families to meet one another. We are all in this together!

BY: KATHY STAGNI

IN THIS ISSUE

THE 2015 CALENDARS ARE AVAILABLE NOW!

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Family Meeting Update

On July 25 and 26th, Children's National in Washington DC had the privilege of hosting the Organic Acidemia Association's family group for two days of learning and fun. OAA hosted this in conjunction with the Fatty Acid Oxidation family group allowing for more sharing and discussion of common challenges and complications among the families who attended.

During this two day meeting, families had the opportunity to exchange stories with each other and hear experts in the field discuss topics ranging from general dietary tips for individuals with organic acidemias to pathogenicity of the disorders to school and learning interventions to maximize abilities. In addition, we had the opportunity to discuss the importance of Emergency protocols/letters, as well as personal, family and legislative advocacy. The highlight was hearing stories from older individuals about how they deal with their particular disorder and learning about their accomplishments. Much fun and learning was had by all. We look forward to seeing you in two years.

BY: DR. KIMBERLY CHAPMAN

Bill Sackter Citizenship Award Winner

Karli, age 25, Propionic Acidemia, is very involved in SAM (Self Advocates Minnesota), shares her story with legislators, speaks to other self-advocates, and direct supports, and has given presentations. She "leads by example, encouraging others to learn about programs and supports and to find their own voice."

Way to go, Karli!

FINANCIAL STATEMENT

OPENING FUND BALANCE	FY 2013	FY 2012
OAA Operating Fund	$ 34,845.54	$ 28,680.86
OAA Research Fund	8,000.00	14,730.04
TOTAL	**$ 42,845.54**	**$ 43,410.90**
CURRENT YEAR CONTRIBUTIONS AND INTEREST		
OAA Operating Fund	$ 31,865.00	$ 67,788.50
OAA Research Fund	7,514.00	4,770.20
TOTAL OAA	**$ 39,379.00**	**$ 72,588.70**
PROGRAM EXPENSES		
Newsletter	$ 6101.54	$ 6792.32
National Family Conference	0.00	47,982.94
Accounting Services	1350.00	1475.90
Office, Internet, Phone, etc.	2814.00	1,963.64
Program Expenses	3974.00	3,409.02
TOTAL PROGRAM EXPENSES	**$ 14,239.54**	**$ 61,623.82**
RESEARCH GRANT		
National Institute of Health	$ 10,000.00	$ 10,000.00
Childrens Hospital		$ 1,500.00
TOTAL GRANTS	**$ 10,000.00**	**$ 11,500.00**
ENDING FUND BALANCE		
OAA Operating Fund	$ 52,471.00	$ 34,845.54
OAA Research Fund	$ 5,514.00	$ 8,000.00
TOTAL	**$ 57,985.00**	**$ 42,845.54**
NET CHANGE CURRENT YEAR	**$ 15,139.46**	**-$ 565.36**

In the fall of each year, after filing the annual 990 report with the IRS, the board of the OAA publishes the organization's financial status. Below is the summary recap for years 2012 and 2013.

The report shows that the OAA ended the year with $57.985 in available funds which represents a net increase of $15,139 over 2012 after all expenses were paid.

Contributions for the year totaled $39,379 which was down from the previous year primarily because 2012 contributions included financial support for the 2012 family conference. Excluding the 2012 conference cost, operating expenses remained relatively stable, increasing only $598 over 2012 spending. This increase is related to our upgraded newsletter format and color printing. As in the past, the OAA made a research grant to support the ongoing work of Dr. Vendetti at the National Institute of Health.

On behalf of everyone associated with the OAA we thank all of our financial contributors – because without their support year-after-year we would not be able to deliver the services for parents and professionals that have become the hallmark of our organization for over a decade.

Mountain States Genetics
Regional Collaborative

The Mountain States Genetics Regional Collaborative (MSGRC) is conducting a survey of families with metabolic disorders and metabolic practitioners on the topic of emergency preparedness. Since emergencies can range from natural disasters to insurance coverage delays, from a house fire to a disruption in supply of a metabolic formula or food, we are seeking YOUR input on how these different types of emergencies may impact you and how to best prepare for them. The short survey (3min) can be taken online at this address (English and Spanish version): *www.msgrcc.org/survey.html.* Anyone may take the survey, but we are particularly interested in the results from the states in the region our collaborative covers: Arizona, Colorado, Montana, New Mexico, Nevada, Texas, Utah and Wyoming.

Thank you in advance for your time and please feel free to share with any other families or practitioners who may be interested.

KRISTI WEES, MSGRC SOCIAL MEDIA COORDINATOR | P: 281-831-3481

Dylan: Propionic Acidemia | Age 11 months

Dylan was born on October 12th, 2013 in Waconia, Minnesota, weighing in at 8 pounds, 2 ounces. After Dylan was born, the doctors noticed that he had a lower than average body temperature, so they brought him back to the nursery to warm him up. He was brought back to us, and from there on out for two days, we experienced a normal, healthy little boy, or so we thought.

In the early morning hours on October 15th, only 15 hours since we had been discharged from the hospital as a family of 3, Dylan was acting strange. He was very sleepy, and seemed cold to the touch. My husband, Adam, and I took his temperature and he was at 95 degrees. Knowing that wasn't normal, I called my sister-in-law, who is a NICU nurse and she told us to try doing skin-on-skin to warm him up, and if that didn't work, to probably call the on-call pediatrician. Much to our dismay, an hour passed and he hadn't warmed up at all. I called the on-call pediatrician and he told us to watch him over the next several hours, if he was still cold and lethargic and didn't want to eat, we could wait to bring him to the pediatrician office that opened at 8am, or we could bring him to the emergency room. About an hour later, my husband picked Dylan up to bring him to me to try and feed, and his arms fell limply behind his body. It's an image that is burned into my mind. We knew at that moment something was wrong, so we packed him up in his car seat and drove him to the emergency room. Once there, they looked him over, and told us that since babies can't tell us what's wrong, they would need to do blood tests and a spinal tap to narrow down what was going on. I remember the ER doctor telling us it was hard to watch little babies get pricked so he told us to go wait in another room (little did I know I would witness far more worse that these pokes in Dylan's life to come). Dylan's breathing also started to become extremely labored; he was really trying hard to get each breath in and out. I don't remember how long we were in the room, but I do remember the doctor coming and telling my husband and I, they didn't have any results back yet, but they believed he needed to be transferred to a Children's hospital in Minneapolis, to put him on a ventilator, because he was getting too exhausted from working so hard to breathe. He left the room, and I lost it, a ventilator, for my little baby? What was wrong? Later the doctor came back and said, he believed they may be able to just use oxygen, so they were transferring him to their NICU, to see if we could get it under control. It was then, that the waiting game began. They did multiple blood tests, at one point coming to the conclusion that he was just dehydrated. His blood sugar was very low, and they believed he just hadn't eaten enough. Hours passed by, and we were waiting for the neonatologist that did his rounds around the more suburban hospitals, to arrive and look at Dylan.

Around lunch time, the doctor came in and looked at him and told us he believed Dylan still needed to be transferred to the Children's hospital to be put on a ventilator because the oxygen wasn't enough. As he was telling us this, a nurse walked in, handed him a piece of paper, to which he looked at, replied "oh my gosh", and left the room. We were freaked out, but didn't think too much of it. Minutes later he came back in and told us that Dylan's ammonia level was 900. He looked at our very confused faces and told us that this was very, very serious, that the normal range was 10-35, and that Dylan may not make it. I remember being numb, to the idea that my brand new baby could die. The doctor left to set up an ambulance to take Dylan, not to the Children's hospital anymore, but to the University of Minnesota Children's hospital, because he needed special treatment, only available at the University. He needed to be placed on dialysis.

I rode in the ambulance with Dylan, and those were the longest 45 minutes of my life. I remember thinking he was going to die in the ambulance, that there was nothing I could do; I just had to sit up in the front seat and pray. Once we arrived at the hospital, it was like a scene out of a movie, all these doctors swarmed us, telling me they'd been waiting, explaining what was going on, needing me to sign consent forms to start dialysis. Telling me that doing dialysis on a 3 day old baby was very risky, but what other choice did we have? By the time we arrived at the hospital his ammonia had climbed to 1200. My husband and I, and our families, were ushered into the family waiting room where we waited to hear word on Dylan. It was at this time we were introduced to our metabolic doctor. She came and met with us and described what she believed Dylan had. A rare genetic disorder, where he could not break down protein correctly, and instead of breaking it down, he would only break down to a certain point and then the bad things (propionic acid and ammonia), would back up in his system. With it being as high as it was, it was poisoning his organs. They told us they believed his brain was swollen and they couldn't be sure what

brain damage he had received from the high ammonia, they would take ultrasounds and an MRI, which both came out fairly good, but really time would tell.

Hours later dialysis began and a nurse came in and said the words, I will never forget "I know this has been the worst day of your life, but I wanted to give you good news, Dylan's ammonia is 90"! As fast as he got sick, he got better just as quickly. They were able to rush Dylan's newborn screening results and that confirmed his diagnosis of Propionic Acidemia. The doctors now had a diagnosis and were able to treat him. As the days passed in the ICU, his ammonia stabilized, they were able to start him on a low protein diet of Propimex and breast milk, he did really well and we were able to go home after just 7 days in the ICU.

Life with Dylan after that seemed to go very well, and to us was "normal." He was a good eater, always ate the amount of protein and calories he needed to get in a day and was developing normally. I would check his ketones in his urine daily (our doctors thought I was a little crazy for checking so much, but it was my indicator something was off), and they were negative until he was 5 months old. Dylan started getting trace to small ketones in his urine almost daily. We would try to push more fluids, but they would still go back up. He was eating all of his bottles and acting completely normal. However, once we saw ketones, we would bring him in to the emergency room and his ammonia would be high, in the 100's. The scariest part was, he never acted different, never showed signs his ammonia was high, except for the ketones.

After being in and out of the hospital for weeks at a time between February and May, our metabolic doctors decided to start him on Carbaglu, to help keep his ammonia in check. When we were discharged from the hospital in late April after starting Carbaglu, we met for a follow up appointment with our metabolic doctors. It was at this appointment that Dylan's doctor sat us down and told us she believed Dylan needed a liver transplant. You see, they were never able to tell us for certain if Dylan had a more severe case of PA because after genetic testing was done, it came back that both of his mutations had never been seen before. So we had to wait and see how he did. We were shocked, never had we thought liver transplant would be something we would be discussing for Dylan. My husband and I went home and for a few weeks thought, prayed, cried, researched, heard stories from other parents that had gone through this, and ultimately decided that we didn't want to wait until another crisis happened and he had brain damage or worse, we wanted Dylan to remain Dylan. So on May 8th, when Dylan was 7 months old, we placed him on the transplant list to get a new liver.

On July 24th, we got the call that they had a new liver for Dylan. We dropped everything and raced to the hospital where they did the pre-surgery prep work, prepared us, and waited for word as to when the organ would be in Minnesota and when surgery would start. On July 26th, the surgery happened. My husband and I walked Dylan down to the pre-op room and handed him over to the transplant team. We were guided to the family waiting room where we waited with our families for 8 very long hours. When the surgeon came out, with a smile on his face, and told us it had gone very well, it was such a relief. We were taken to see Dylan, and as scared as I was to see him, when we did, he looked so good. Yes, he was hooked up to so many tubes and lines, and he was swollen, but he looked just like our boy. We stayed in the hospital for 18 days as Dylan recovered. His body accepted the new liver, and one of the best moments of our lives, was when our metabolic doctor came in and told us that the organic acid tests they had taken on Dylan after surgery had shown he had no propionic acid in his body! What a miracle.

It will be a long road, and like many have said, you do trade one thing for another with transplant. Dylan will be on anti-rejection medications his whole life. There's the fear that he may go into rejection at any time, but if caught early enough, it is very treatable. And here in Minnesota, with our doctors, they will keep a very close eye on him. We also don't have much research on if this liver will last his whole life, or if he would need a new one eventually, but at the same time, we don't have a ton of data on what PA does to the body long term. Our metabolic doctors are being very cautious, increasing his protein intake by 30% each month, and testing his propionic acid to make sure it remains negative with each increase. He is still on carnitine, but eventually may be off of that. He already is eating things he wouldn't have before and soon they said we could introduce dairy! The change in him since transplant has been tenfold. Before he had low tone in his upper body and wasn't sitting very well. Now he sits so well, started army crawling the other day, is talking more than he ever was, standing on furniture and a very happy little guy. Although it was the toughest decision my husband and I have ever made, this was the right decision for us, we wanted Dylan to lead the best life he could, and even though there were so many risks, and we don't know 100% what the future will hold, it was worth it, because he is such a happy and very healthy almost 1 year old!

If you would like to follow along with Dylan's progress, or would like to contact me with any questions you can follow his caring bridge site at *www.caringbridge.org/visit/dylanjaehnke* or e-mail me at *ellso015@gmail.com*.

BY: JENNI AND ADAM, WACONIA, MN

OAA FEATURED ARTICLE

Liver Transplantation for Propionic and Methylmalonic Acidemias

JERRY VOCKLEY, M.D., PH.D.

Professor of Pediatrics, University of Pittsburgh School of Medicine

Professor of Human Genetics, University of Pittsburgh Graduate School of Public Health

Chief of Medical Genetics, Children's Hospital of Pittsburgh

Liver transplantation (LTx) was initially developed as a therapy for liver diseases known to be associated with a high near-term risk of death. However, LTx for inborn metabolic diseases is based upon a different set of criteria. It is of use for any disorder in which toxic metabolites can affect any organs through the systemic circulation. In this setting, a transplanted liver can correct metabolic balance in other organs. As risks of the procedure have decreased and post-operative outcomes have improved, LTx has evolved into an attractive approach for a growing number of metabolic diseases in which the procedure can be life-improving rather than strictly life-saving, blurring the line between standard medical management and a more aggressive surgical therapy. In this setting, the risks and benefits of LTx must be placed in the context of current and potential medical advances. Ultimately, it is critical to have a relatively complete understanding of the biology of the disease to predict the potential impact of LTx on the body.

Propionic acidemia (PA) and primary methylmalonic academia (MMA) are organic acidemias resulting from defective breakdown of the amino acids isoleucine, valine, methionine, and threonine due to mutations in the genes for propionyl-CoA carboxylase or methylmalonyl-CoA mutase, respectively. MMA is additionally present in several inborn errors of cobalamin (vitamin B12) metabolism. Severe forms typically present with severe hyperammonemia, ketoacidosis, and neurological problems, including coma very soon after birth. To minimize neurological sequelae, intensive clinical management, including aggressive treatment such as dialysis or hemofiltration, is required. Despite early diagnosis and maximal metabolic control, many patients develop considerable neurological, psychological, cardiac, and renal complications [36, 39].

17 cases of transplant of propionic and 35 of methylmalonic acidemia have been reported in the medical literature. Follow up ranged from 2-120 months. Clinical experience remains relatively limited but is encouraging. Successful LTx appears to improve metabolic control, resulting in better quality of life with less strict dietary restrictions, and positive effects on development. Heart failure has improved if present. However, other consequences of the diseases can still occur, including CNS complications such as metabolic stroke its incidence and severity of metabolic strokes is dramatically decreased. Renal failure can still occur in MMA and so a combined liver kidney transplant should be considered in this condition, especially if renal disease is already present. Benefits must also be weighed against the risks of long term immunosuppression.

The use of solid organ LTx to treat liver-based metabolic disorders is limited by a severe shortage of donor organs, the risks associated with major surgery, and the low, but real, long-term risk of graft loss from rejection.

Hepatocyte transplantation holds promise as an alternative to organ transplantation, and numerous animal studies indicate that transplants of isolated liver cells can correct metabolic deficiencies of the liver. Clinically, the procedure involves isolation of cells from livers rejected for solid organ transplant, which are then transplanted via the portal vascular system into the liver [75]. This procedure is far less intrusive than replacement of the liver. Since the native liver is not removed, the transplanted hepatocytes need only improve the single enzyme deficiency and need not replace all hepatic functions. Since even a full liver transplant doesn't reduce metabolite concentration to normal in blood in patients with PA and MMA, the role of hepatocyte transplant remains to be demonstrated.

The efficacy of LTx for metabolic diseases has been demonstrated through single- and multi-center reviews as well as in reviews of national databases, achieving a >82% survival rate at 10 years. The single center experience at Children's Hospital of Pittsburgh provides outcomes over thirty years. In that time, two-hundred and eighty-five children underwent pediatric LTx for metabolic indications. The mean age at transplantation was 7.6 years (16 days to 23 years). Forty-three children underwent re-LTx at a mean of 2.3 years (2 days to 18.2 years) post-transplant. While historically, 70% of transplanted patients are still alive, results over the last 10-13 years have demonstrated significant improvement in survival. Of 100 patients receiving transplants over the past decade at CHP, only three died (two of infection and one of

suicide) and only one required retransplantation, with patient survival over the past 10 years currently at 97%. Longer follow-up will be needed to recognize late appearing concerns in patients and families. Immunosuppression and current research on how to reduce its impact is a major component of the program in Pittsburgh. Clearly, clinical decision-making is best undertaken by a discussion of the best available long term results of transplant in the context of a patients specific circumstances.

The shortage of available livers for transplantation is an important issue to consider with the use of LTx for metabolic disorders. While the use of living donors is becoming increasingly popular, a potential complicating issue is that parents of children with PA and MMA are carriers for the conditions, and there is a 2/3 chance that their siblings are carriers. However, since parents have no symptoms, 50% of normal activity is likely to be sufficient to improve metabolic control.

In summary, LTx has been revolutionary and life-saving for some metabolic disorders. Initially viewed as a rescue procedure for such conditions, the risk of death or disability due to many inborn errors of metabolism now outweighs that of a transplant. Thus the role of transplant in treatment of PA and MMA will likely continue to evolve and increase.

Max: CblX | Age 10

In September 2011, Max's doctors took a blood sample from me and Steve. That sample would be tested and DNA extracted to try to pinpoint exactly what Max's metabolic disease was.

One year later, we heard about that testing again. Max was in the hospital after yet another intestinal surgery, and had a long recovery. During that time, we met many times with his metabolic doctors and talked quietly about their preliminary findings. I spoke only briefly about it on Max's blog. Only that we were hearing some interesting new things and would learn more as time went on.

This past year, we've certainly learned more about the findings, and today we can officially announce the name, and present the paper on Max's disease.

This article written on this new disease was released by The American Journal of Human Genetics, along with the CU Press release. Max is Subject 1 in the article. The disease was found in him first, and then tested against other subjects to see if they also matched their findings. This new disease is called Cobalamin X, or CblX. I just typed CblC, which will be a habit I will have to break, as for nearly 10 years it's been what we knew Max to have.

It was Max's doctors and the researchers at the University of Colorado, School of Medicine, Human Genetics Lab who found this mutation. They named it, along with collaborating labs around the world; including Max's research doctors at NIH, and the doctor in Canada which first got Max's biopsy at 4 months old to diagnose. We thought it needed to have "Max" somewhere in the name, but as the gene is an X linked recessive inheritance disease, that's what they went with. We'll, Their findings are so contrary to what we've always known Max's metabolic disease to be. We were told when Max was diagnosed at 4 months old; he got two bad copies of genes from me and Steve, recessive genes we carried, which were made dominant in Max. We were told he was missing essential enzymes in the processes of the cobalamin cycle which made his body build up deathly levels of acids. We were told he didn't have the gene mutation the other children with CblC had, MMACHC. This lack of MMACHC gene is why they've kept looking all these years. This brought them to the discovery of Max's new disease, CblX.

What they have found, Max has one bad gene called HCFC1. Max has a normal MMACHC (CblC) gene which theoretically would work normally. His HCFC1 X-linked defect causes a global disruption to the cobalamin pathway by not promoting MMACHC accurately. This is what causes the buildup of acids, not that he's missing enzymes in the Cobalamin pathway.

If that sounds like a bunch of gibberish, it really boils down to this: Max has one bad gene that flipped a switch in his metabolic process and turned some very important lights off, causing all his metabolic and neurological problems.

We know now that the gene is not autosomal recessive (a bad gene from each parent), but is an X linked recessive inheritance disease. I've written that twice now, so it must be important. It is a bit, really. This is the first time in this type of metabolic disease where they are finding the diseases showing up from one parent, and in one case - from neither parent. In Max's case, CblX was passed on from me, to him.

[continued page 8]

[Max continued from page 7]

Go back to 9th grade Biology with me for a minute. Girls have 2 X chromosomes; boys have an X and a Y. When the mother has 2 X's, and one of those X's is bad, she has another one to cancel the bad one out. Her son does not have an extra X to cancel out the bad. In my DNA, that one gene, the HCFC1, is bad...corrupt...flawed. When I passed my DNA on to Max, it copied that bad HCFC1 gene, and wham - gave him CblX. If my baby had been a girl, she would not have CblX.

Once we realized the genetic defect did not come from Steve, we started barking up my family tree and had my parents and siblings tested. None of them had the same gene mutation, which mean it started de novo, or spontaneously in me. This simply does not happen in these types of metabolic diseases, Organic Acidemias. It is a first time finding, and one that is really important in the world of genetics. It's one big fat, "who knows why this happened; but it did", and the result is Max's disease.

What does all of this mean? Nothing and everything. It's like when Max was born; we were given a huge box of puzzle pieces and knew we were only looking for one puzzle piece. We've found that puzzle piece, so now we can start putting the puzzle together. Treatment will not change in Max.

We still have no prognosis, as he's the first one (and oldest they know of) with the disease. Now that this is common knowledge, we hope we can find the other boys. Yes, it's a "boys only" club. So, in Max, not a lot is changing. Just the four letters after his name; CblX.

For Children's Hospital Colorado, and University of Colorado School of Medicine, plus the collaborating labs around the world who worked on finding this gene and naming the disease, it changes everything they've known up to this point about this type of disease. It changes the way they look at the cobalamin diseases, and also what this HCFC1 gene does. It will mean more research; years and years of research. It means Max has played a very important role in changing science. In that regard, it's a pretty big deal. And one we, as a family, are happy to be a part of. Every parent wishes for their child to one day make a huge contribution to society, and the world. Max has done that by simply being his amazing self, and his unique make-up is changing the way scientists and doctors will look at how these diseases work.

We've been digesting this information for a while now, so I don't want to regurgitate it all out at once here. We will be discussing it more, and more as we get more information to share. But the long and the short of it is, this is Max, CblX.

DEANA W., COLORADO, MOM TO MAX, CBLX
WWW.MAXWATSON.ORG

UPDATE: Propionic Acidemia Research

ADAM GUENZEL, PREDOCTORAL FELLOW,
VIROLOGY AND GENE THERAPY PROGRAM

MICHAEL A. BARRY, PH.D., PROFESSOR

MAYO CLINIC COLLEGE OF MEDICINE

BACKGROUND

Gene therapy research in the Barry Lab at Mayo Clinic has been supported with funding from the Organic Acidemia Association, the Propionic Acidemia Foundation, as well as by the Mayo Clinic Center for Regenerative Medicine. Our work has focused on developing a mouse model of propionic acidemia (PA) that can be used for basic study of PA disease and development of gene therapy vectors for treatment of PA. The original mouse model generated by Dr. Miyazaki at UT-Southwestern lacked both copies of the PCCA gene that encodes one subunit of the propionyl-CoA carboxylase (PCC) enzyme. This lack of PCC meant that the mice only survived 36 hours making analysis of disease processes or testing of therapies difficult.

To create a more compatible model, we introduced a human gene encoding PCCA that had an A138T mutation that was identified in a patient with propionic acidemia by Dr. Ugarte's lab at Universidad Autònoma de Madrid. In collaboration with Dr. Jan Kraus at the University of Colorado, we determined that the A138T mice have approximately 2% of normal PCC enzyme activity in their livers. Unlike the original PCCA mice with no PCC activity, most of these A138T mice survive to adulthood, but have very similar elevations of the same blood metabolites seen in propionic acidemia patients. These include elevations in propionylcarnitine and methylcitrate as well as increases in glycine, alanine, lysine, and ammonia. We have also observed evidence of cardiac dysfunction and possible heart failure in the mice suggesting that they also share this symptom.

Our findings highlight the diverse nature of PA presentation. Elevations in circulating propionylcarnitine and methylcitrate are nearly universal in affected individuals, but other aspects of the disease are observed less frequently. Different organ systems are implicated in

different people, for instance neurological symptoms are common and manifest as seizures, developmental delay, lethargy, and hypotonia. In the heart it is common to see arrhythmias and cardiomyopathy even in young PA patients. Many of these symptoms are worsened by noncompliance with protein restricted diet regimens or stress to the body caused by infection.

Although dietary treatment has greatly improved the prognosis for PA patients, few other treatment options have been developed. Liver transplantation has emerged as a viable therapy option for PA, but transplant operations carry a certain degree of risk themselves. Anesthesia to begin the operation may by itself make this approach unsafe for certain PA patients. After liver transplantation, life-long immunosuppressant drugs will be needed to prevent rejection of the donor liver. Immunosuppression may also increase the risk of infections that may also drive metabolic crises.

Given these issues, we have worked to develop safer and less invasive treatment options based on gene therapy with viral vectors. To date we have treated adult mice with adenoviral and adeno-associated virus (AAV) vectors expressing the gene for human PCCA. We demonstrated in an article titled "Generation of a Hypomorphic Model of Propionic Acidemia Amenable to Gene Therapy Testing" published in the journal Molecular Therapy (2013) that both of these gene therapy vectors significantly reduced propionylcarnitine and methylcitrate levels in the blood of the mice within one week of treatment. We are pleased to note that propionylcarnitine and methylcitrate levels have remained low for over a year-and-a-half after treatment with a single dose of AAV in male mice suggesting that the therapy can last for long periods.

One practical note that may interest parents of children with PA is the fact that gene therapy in the mice appeared to rapidly improve the ability of the animals to consume normal protein-containing food. Indeed, within one week of therapy, the body weights of the animals increased drastically. This bodes potentially well for this approach having positive day-to-day impact should we be able to translate this towards treating PA patients.

NEW STUDIES

The varied presentation of PA across several organ systems has caused some investigators to examine where the cause of these symptoms lie. Previous studies have shown that certain protein complexes in the mitochondria of heart tissue are lower than in individuals without PA. Since the mitochondria are responsible for providing most of the energy used by cells in the human body it is thought that this could lead to a lack of energy available to the heart and result in cardiomyopathy. It is also unclear exactly what effect circulating levels of propionylcarnitine and methylcitrate have on the body and we are not sure to what degree different tissue types contribute to the circulating levels of these compounds.

Our most recent study using our A138T PA mouse model was designed to help clarify some of these questions. In September of this year (2014) we published a new research article in the journal Human Gene Therapy titled "Effects of Adeno-Associated Virus Serotype and Tissue-Specific expression on Circulating Biomarkers of Propionic Acidemia." Our group and others have observed that different serotypes of AAV are more apt to deliver genes into the liver, heart, or cardiac and skeletal muscles in mice.

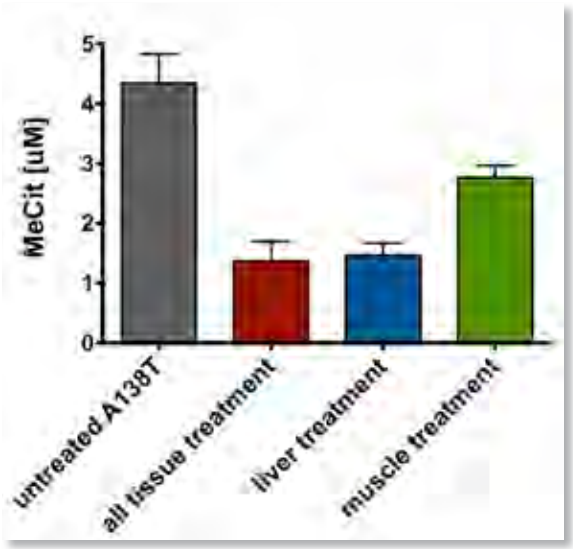

Figure 1. Methylcitrate correction after tissue-specific treatment. Methylcitrate levels were measured in the blood 45 weeks after injection with AAV vectors capable of expressing PCCA protein in all treated tissues, or specifically in the liver or cardiac and skeletal muscle.

For example, AAV1 is better at delivering genes into muscles and AAV8 is better at delivering genes into the liver. We made these vectors totally specific to the muscle and liver and then compared how well they could treat the PA mice. Under these conditions, both vectors improved metabolic levels, but the liver-specific gene therapy reduced systemic metabolites better (Figure 1). In many ways, the AAV8 liver-specific gene therapy is analogous to transplanting the liver, except we perform a simple injection rather than invasive surgery and do not have to apply immune suppression. Conversely, gene therapy is more experimental than transplantation, so safety still needs to be evaluated.

[continued page 10]

[Propionic Acidemia Reseach Update continued from page 9]

Reduction in the methylcitrate levels shown here is encouraging because it is hypothesized that high levels of methylcitrate in tissue could be a possible cause for the energy deficiency mentioned in the heart and has been correlated with high ammonia levels in the brain as well.

While liver-targeted gene therapy reduced metabolites in the blood better, in more recent work, we have found that the muscle-targeted vector was markedly better at repairing the heart. For example, AAV1-PCCA corrected signs of cardiac dysfunction, but AAV8-PCCA did not.

These data suggest that gene therapy that repairs PCC in as many tissues as possible is better than therapies that only repair it in one site. This is consistent with observations that liver transplantation can blunt certain symptoms, but may not always improve others like cardiac effects in PA patients.

OUR FUTURE PLANS

Since the liver is the main metabolic organ in the body, it will need to be treated by gene therapy or by transplantation. These studies also demonstrate that there are potentially harmful compounds being produced by the muscles and that gene therapy in the muscle reduces systemic metabolite levels, but also reduces cardiac symptoms. These data suggest that tissue targeted gene therapy or transplantation are not the best approach to address the spectrum of PA disease effects in different tissues. Therefore, we are moving forward to improve AAV vectors that deliver genes to many tissues after intravenous injection.

In addition, we are working to use the mice to better understand the neurologic consequences of PA and to determine if direct neurologic gene therapy will be needed. Our PA mice have a number of symptoms that indicate that the disease is impacting their brains. Since we can't speak to the mice, these symptoms are unfortunately difficult to assess. We are therefore embarking on a number of studies to explore if the A138T mice are a good model of the neurologic aspects of PA. The mice have high levels of ammonia in their bloodstream and we are working to determine how the circulating ammonia or methylcitrate produced locally in the brain may affect the disease. There are similar questions to those we have addressed in the heart that must be addressed in the brain as well. Do we need to treat the brain specifically or will systemic treatment of the liver and muscles alleviate brain symptoms? What is the most effective way to treat the brain with gene therapy? Fortunately the AAV vector system will allow us to explore different options, and we have excellent collaborators that are helping us address these issues.

Kristy: Propionic Acidemia | Age 49

Well, it is time to check in since it's been a while. My husband decided after 12 years of marriage (the day after) that he no longer loved me nor wanted to be married. He'd actually decided this much earlier but told me this the day after our 12th anniversary. One reason is that I am sick too much. I write this because this is the newsletter about our diseases. My husband (ex now) donated his kidney to me seven years ago with the expectation that I would get healthier and would be able to work again. That did not come true. He did not like being the one making all the money in the relationship. There were other issues as well; but needless to say, we got a divorce almost a year ago. I was devastated and it was only for friends, family and faith that I got through it. But, I cannot believe where I am now. I am discovering ME!

I am back to my maiden name! Plus, I have taken my dog and cat and moved to Las Vegas, Nevada! It is beautiful here with the mountains and, yes, I even love the heat. I have just purchased a 3 bed/2 bath single-family house. So, excited to start updating and decorating to make it mine!

The Ex does not know where I am and can only reach me by e-mail if he so desires: which he has not tried since I told him to "Please Leave Us Alone." With God's help, I am on this new adventure.

KRISTY, LAS VEGAS, NV | BEWAREOFHARE@YAHOO.COM

JEN SLOAN FACILITATES THE YOUNG ADULT DISCUSSION AT THE 2014 CONFERENCE

Are you interested in participating in research?

Some folks are excited to participate in research protocols; others are frightened by research. In general, participating in research in rare diseases can be as simple participating in a registry which records how many individuals have a particular diagnosis or their complications from the disorder. Research can also be more involved and study a particular intervention or medication. One thing to remember about rare disorders such as organic acidemias is that there are many things we do not know. For example, we are not entirely sure how common some organic acidemias or how common certain complications are (for example, cardiomyopathy in Propionic acidemia).

If you are interested in participating in research, Dr. Kimberly Chapman and her colleagues at Children's National want to announce that they are a site for the European Registry and Network for Intoxication Type Metabolic Disease (EIMD), more specifically for the organic acidemias, Propionic acidemia, Methylmalonic acidurias (from MUT, MMAA, or MMAB mutations), Isovaleric acidemia and Glutaric acidemia I, as well as the European Network and Registry for Homocystinurias and Methylation Defects (EHOD) which includes classical and B6-responsive homocystinurias, Cobalamin C/D/E/F/G/J disorders, severe methylenetetrahydrofolate reductase and dehydrogenase deficiencies, Methionine adenosyltransferase I/III, Adenosine kinase, Glycine N-methyltransferase, s-adenosylhomocysteine hydrolase, and more.

What are EIMD and EHOD? These are registries for individuals with the above organic acidemias and related disorders. The goal of the registry is to create a database used to determine how common these disorders are, what the common complications are, at what ages these complications are occurring, in addition to cataloguing the current management approaches used. To do these things, these registries require some information

from the participant's medical history, and will follow the participant over time. The participant's metabolist/geneticist will treat the participant exactly as they would ordinarily and update the Principal Investigator (in this case, Dr. Chapman) about the participant's treatment and hospitalizations. This information will be entered by Dr. Chapman or her team (or your local Principal Investigator) under a number instead of the participant's name into a database that is housed at the university in Heidelberg Germany. If you would like more information about becoming a participant or having your care become a participant, you can contact Dr. Kimberly Chapman or one of her genetic counselors, Katie Crosby or Sandra Yang, preferably by emailing KChapman@childrensnational.org, KaCrosby@childrensnational.org or SYang@childrensnational.org or by calling 202-476-6812. Either can direct you to a local site for the studies or discuss it with you and your/your care's metabolist/geneticist.

In addition, EIMD has a website: http://www.e-imd.org/ as does EHOD, http://www.e-hod.org/ from which you can get more information about the studies. These websites also have some patient and family guides for some of the disorders. There are plans to increase the disorders covered by the guides and expand the languages available so check in periodically if your disorder or language is not covered as of yet.

OAA BOARD: CAY WELCH, KATHY STAGNI AND MENTA PITRE AT THE 2014 CONFERENCE

2014 CONFERENCE VENDER - VITAFLO

Maren: Propionic Acidemia | Age 2½

Maren Winter was born on February 13, 2012. She weighed 8 pounds 6.5 ounces and was 21 inches long. She had a bit of peach fuzz for hair and was chubby as chubby gets! Maren was home for two weeks growing, eating, and sleeping. We received a call on a Saturday afternoon while we were at a birthday party for a friend's daughter. The doctor was local and told us he was calling to check up on Maren's well-being. We let him know everything was well. He then stated he was calling due to an abnormal value on newborn screening. Apparently, Maren had elevated C3 numbers. This doctor could not really tell me what that meant at the time. He said we would be contacted by Children's Hospital later that day, and, we were. But, before they called, I made the mistake of researching "C3" and its indications. I was able to read and learn about some conditions called Methylmalonic Acidemia, Propionic Acidemia, and biotinase deficiency. So, when Children's did finally call, I understood all too well the words that slipped out of the counselor's mouth…."positive for Propionic Acidemia."

We were at Denver Children's first thing Monday morning. We were educated about the disease and were taught how to care for Maren. We were absolutely devastated. I don't even truly remember the entire appointment because I was so grief-stricken and shocked. These early days were the darkest most tortuous moments of our lives. There were times I cried for my daughter, and there were times I cried for myself and the family I thought I would have. I had some extremely selfish moments where I felt angry that this was "happening to me." You couldn't pay me any amount of money to return to these moments in my life. They have been our darkest hours.

Maren had a fibroblast assay done and was shown to have at least 1.8% residual enzyme. She has one mild mutation, a missense mutation. She also has one severe mutation, a frameshift mutation. Both mutations have been seen independent of one another in two other cases but not both together in one child. Both of those children were considered to have the late onset variety of Propionic Acidemia. Maren has not had hyperammonemia issues. She has been sick many times with little bugs here and there but never anything too serious as of yet. She has had one hospital stay due to a stomach bug. All milestones have been met or even exceeded. Maren was walking at 10 months and running at 11.

It has now been two and a half years. Maren has been doing very well. She gets a monthly blood draw now to check her amino levels. She eats by mouth approximately 8.5 grams of protein through food with the rest of her protein being in her metabolic formula. She takes 23 mLs of carnitine as well each day. She is only now beginning to tell others that she has "PA" and is beginning to decline foods that are not part of her diet. Just last night she told her 8 year old brother, Lyric, "I don't eat that. That's not for me. This is for me." Maren showed him her bowl of rainbow sherbet while her brother ate his vanilla ice cream with chocolate.

Lately our minds have been preoccupied with the discussion of liver transplantation. Yes, WE, the parents of a more "mild" child (also called a "manageable case") are considering liver transplant. We have researched and researched and researched some more. We have spoken with adult PAs and parents of PA children whose children were deemed mild and not eligible for a transplant. There were some with regrets for not having advocated more aggressively as their "mild" children declined, died, or lost faculties. We also spoke to as many parents of children who received liver transplants as possible and found that by and large many are thriving and are living a life symptom free. Mild or not, our daughter is at risk every day.

We are considering auxiliary liver transplant for Maren. Auxiliary liver transplant would have Maren retain her own whole liver while grafting a section of a cadaveric liver to hers. She keeps her perfectly healthy liver in its entirety and receives an additional section that will make the enzyme she needs. There is a lot to consider, and we have not made any final decisions.

The support my family has received from the OAA has been our main support. Without the parents and families we have come to know and love, I don't know how we would ever be able to do this. Thank you, friends!

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An MMA Journey from China to US

Our First Child Died

Caroline and I are very happy to wait for our daughter, Emma, to come. Every night, I told stories to Emma, though she is still in her mother's body. One night, Caroline's water broke. We sent her to hospital and the next day, we met Emma. We love her so much. She is beautiful, she is like an angel! I still remember that this moment is the happiest time in my life.

Then, on the seventh day, Emma was in coma. We cannot wake her up. We sent her to a children's hospital in Beijing and then we learned there is too much bacterial in Emma's blood. Even after a transfusion, doctors still cannot save her. She died, in her third week.

Our Second Child Faces the Same Problem

Doctors guess Emma's death is a result of blood conflict between my blood B and Caroline's blood O. After taking over 18 months' Chinese medicine, our son, Jimmy was born. On the third day after his birth, he began to vomit. It was projectile vomit. Doctors took some blood sample from him and send Jimmy to NICU. The second night, my mobile phone waked me up in 12pm. It is the call from NICU. The doctor said, "Your son has MMA."

"What is MMA?"

"I think you should go search on the internet yourself. But let me tell you first, it is not good."

"Thank you! I will do it now."

To avoid waking up Caroline, I sit in the toilet and use my mobile phone to search MMA. "MMA Make My Family Broke!" "Please Save MMA Families. Government! " After reading those articles from Internet, My mind was blank. According to their experience, I am going to take care of a paralyzed son, for the rest my life.

I didn't tell Caroline until the morning. She is very calm after she learned this. Caroline said, "even if Jimmy is paralyzed, we are going to take care of him forever."

Doctor Suggested Us to Give up Jimmy

Doctors don't think it is a good idea. A doctor told me privately, "I think you should give up this baby. You are very young. I think you can have a healthy one in the future."

"How to give up a baby?" "It is easy. Take your baby home and stop feeding him. When he dies, bring the body back, we can handle the rest."

"Thank you!"

I told myself, "I cannot murder my son. He is my son! He deserves the right to live!" My parents flew from Xi'an to Beijing; they still think the baby will be OK. They didn't do any search on Internet. Finally, they decided to pick up Jimmy from hospital. My father's first impression on Jimmy is "what an energetic baby, he is good."

Jimmy is Like a Normal Baby

Yes, Jimmy was good after coming back from hospital. Caroline breast fed Jimmy and Jimmy sleeps well. My parents began to doubt Doctor's diagnose. Everybody is happy about Jimmy. I was the only person still doing research on Internet. I thought this story is not going to be easy.

I found an online group in China. There are over 300 families registered in the group. I joined the group and began to share information. Their suggestion to Jimmy is, "Don't be careless about MMA. You should talk to Doctor Yang. She is the specialist in this field."

When Jimmy is one month old, we took him for the first MMA appointment. Doctor Yang think Jimmy needs B-12 injection twice a week and needs to start taking L-carnitine every day. She gave us an IV injection prescription and said, "When Jimmy's acid level goes up, he will began to vomit, give him IV".

We Couldn't Stop His Vomit

I don't think Jimmy will ever need IV, since Jimmy looks so good in the first 6 months. Then everything began to change. Jimmy start to vomit on his 9th month, but IV injections couldn't stop his vomit.

From his 9th month to 2nd year, Jimmy vomited over 200 times. He got an IV injection right after his every vomit. Doctor Yang said, there is nothing we can do besides IV fluids. During that period of time, you can easily find needle holes in Jimmy's hand, feet and forehead. As a 30 lb. baby, he lost close to 8 lb. in several months.

[continued page 14]

[Emma & Jimmy continued from page 13]

He was so thing and so fragile. Jimmy lied on my shoulder and is very weak. In order to calm Jimmy down, Caroline hold Jimmy all the time when Jimmy was having IV shot. After every shot, Jimmy began to vomit again, sometimes inside my car, sometimes on the bed, sometimes on our clothes. Our life was a mess.

A Letter to NIH

One night, Jimmy vomited again. All family began to clean his quilt, his clothes and Caroline's cloth. After doing these, I began to search Internet for more information.

At about 2 am, Caroline wake up and asked me, "What are you still doing?"

"I think we should go to America for a medical check."

"Is that even possible?"

"I am writing to a scientist in this field to see the possibility first."

"Where is the scientist?"

"It is Dr. Venditti, in NIH."

Out of my expectation, Dr. Venditti replied my mail and invited us to visit NIH when Jimmy is over 2. To most people in China, seeing doctors in USA is impossible. But we made it!

In April, 2013, we visited NIH for the first time. To us, NIH is like heaven. Jimmy can play in the Children's Inn all day long and there are parties almost every evening. After a series of medical examination on Jimmy, we learned Jimmy's condition very well. Dr. Manoli gave us a lot of advice on how to balance Jimmy's acid and how to feed Jimmy. With the proper medication, Jimmy develops in a very good health condition after coming back.

We Decided to Leave China

We got a new problem. MMA medicine and formula is very expensive. In China, medical insurance never cover the rare disease medication. Every month, our salary is only enough for Jimmy's medicine and special formula. I realized it could be a very big problem. Jimmy's medical expense spent almost all our savings. The only property we still have is our house. If Jimmy needs kidney and liver transplant in China in the future, we will have to sell this house.

"Why not sell this house now and move to US", I began thinking about this bold idea. By using Google, I learned, if I can build a successful business in US and hire a certain number of people, all my family can move to US and enjoy the medical benefit there. After about 6 months preparation and paper work, we got visas from US embassy in Beijing.

Finally, we all moved to Philadelphia, to start our new life. No one knows what is ahead, but our family will stick together and give Jimmy the best life we can.

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Sarahya & Xayvior MMA, Mut 0

Most people think of the fighting sport when I say MMA, but my two children are true MMA champions, and here is their story.

I'm always amazed; always amazed at the power of faith, perseverance, and the power of a fragile little child.....

I will never forget the day my first child, Sarahya, was born. She was so fragile, at only 3 pounds 4 oz., but she was perfect to me. She struggled to grow and survive in my womb, which is why they took her out at only 35 weeks along.

Right away she struggled to survive outside my womb as well. She wouldn't eat, and the formula and breast milk both made her even sicker. No one knew what was wrong. Then after a few days, the newborn screen came back and showed an abnormality, a genetic disorder called methylmalonic acidemia, or MMA. They wanted to run the test again to be sure.

Methylmalonic acidemia, it was such a big and unfamiliar term. Of course I went to google and researched it. I was horrified. As I read about how often this disorder can be fatal, and how it can cause things like kidney and liver failure, mental retardation, low muscle tone, and a continuous list of other lifelong disabling conditions, I just felt completely overwhelmed and in shock.

I never imagined I would ever have a child with a disability. I always pictured having a healthy and happy child; smart, beautiful, ready and able to take on the world and achieve more than I could ever imagine for myself. I think all parents desire these traits for their children. With one diagnosis, between the doctors and a google search, those dreams should have gone out the window for me, but my heart told me otherwise.

At about day 10 in the NICU, the second test came back, and it was confirmed that my baby girl had MMA. I remember the metabolic doctor and the nutritionist came to speak with me. They brought a box of Kleenex into a small room, so I knew right away that this would not be an easy conversation.

They explained to me that MMA is caused by two non-working genes, one from the mother and one from the father. MMA is extremely rare; in fact my daughter was only the second diagnosis of MMA

in all of Nebraska, and the only MMA patient in Omaha when she was born. The chances of a child being born with MMA in the general public was about one and 100,000, (although with increased newborn screening, this number is now more like one in 25,000- 50,000) but between two carriers of the nonworking gene there is a 25% chance. This took me back to biology class when I learned about recessive and dominant genes, but this was something I had never learned about. In fact, most doctors don't even know much about MMA.

So the big question was how this disorder will affect my child's life. Of course I read everything on Google about the chances of fatality, the chances of liver and kidney failure, the chances of mental problems, etc. I was reassured that with early detection and proper treatment, MMA is not always pure doom. Of course they also explained to me that this would not be an easy road, and my child would not be like a normal child. There would be complications, there would be hospital stays, there would be a daily routine of medications and controlled diet. MMA patients do not have the enzymes to break down proteins in the body; therefore they must have a protein restricted diet. This means no meat, no beans, no eggs, limited dairy, and a special formula that I had never heard of, as it is not available on store shelves, or even at the local pharmacy. There was a whirlwind of information being thrown at me, in this tiny room, with a box of Kleenex at my side.

I was simply at a loss for words. I didn't know how to feel, or react. I cried for a while, and used up a bit of that box of Kleenex, and by the end of the meeting, I knew I had to compose myself. I told myself that there would be no place for these tears around my child. If I showed any dismay, any inkling that I might lose hope for her, she would sense that and she would not fight. I had to be strong, so she would be strong. Parents must set the example for their children, and my first example to my daughter would be to be strong and to fight.

Another 4 and half weeks passed in the NICU. Sarahya was started on the special low protein formula, but she still would not take it my mouth, so she had to have a feeding tube inserted. She had a whole other list of complications, not necessarily related to the MMA. Since she was preemie, she had to be in the incubator for quite a while. She also had problems with her stomach becoming distended, so she was on TPN off and on during that time as well. It seemed that for every step forward we took two steps backwards. But she kept fighting, and after six weeks in the NICU she was finally healthy enough to go home.

The day I took her home she weighed 4 lbs. 14 oz. She was the tiniest, cutest little baby had ever seen. She went home with no feeding tube, no extra medical supplies other than a list of medications and her special formula. I had no idea how short of a time this would last.

About a month later the hospital admissions began. It seemed there was always something going wrong. She would not eat well enough by mouth, and was not gaining weight well. When a child with MMA does not eat well enough, their body goes into starvation mode. Just like anyone who tries to starve themselves to lose weight, the end result is a breakdown of muscle rather than fat. When an MMA child breaks down muscle, they are breaking down protein. Since their bodies cannot effectively break down protein, they end up getting very sick. The ammonia levels in their bodies' rise, which often times results in brain damage.

It was a constant battle to keep my daughter from getting sick. Either she would not eat well enough, or she would catch some kind of bug at daycare which would cause her to get very sick and her ammonia to get very high. Every time she got sick it was a very scary situation. I would rush her to the hospital to check her ammonia and they would have to put an IV in to give her fluids, and of course a feeding tube to feed her, and she would have to stay in the hospital for days or weeks at a time. It was a routine that I just became used to, and I accepted it as my new normal. I did not care what it took; I just wanted my child to survive.

At six months old Sarahya had surgery to get a permanent feeding tube, which is called a G button. It was a difficult decision, but the best decision because she had a better solution for her nutritional needs. Also she did not have to have a tube down her nose anymore, and I no longer had to put it down her nose and worry about the risks associated with that. She did great through her surgery and recovered quickly.

When Sarahya was seven months old, she became very ill and her ammonia got so high that she fell into a coma. I believe that was her 13th hospital admission. It was the most terrifying moment of my entire life. I remember that day so well. It was probably around three or four in the morning, and I happened to check on Sarahya and noticed her eyes were rolled in the back of her head. [continued page 15]

[Sarahya (4 years) and Xayvior (1½ years
continued from page 15]

I tried to wake her, but she was unresponsive. She was just lifeless. I rushed her to the emergency room, and the entire time I was driving all I could do was pray. I think I went 70 mph to that hospital, and it was like the streets were cleared for me, probably because it was 3 am.

Anyhow, when we arrived at the hospital they rushed us back into a big room, not like the other ER rooms we had been in before, this one was huge, and bright, and there were medical instruments of all sorts. This room was equipped for true emergencies, for life threatening situations. I stood and observed as about a dozen medical professionals stormed that room, attaching my baby to all sorts of medical equipment. They drew blood on her and started an IV, and she didn't make a sound or move at all. I never thought there would come a day that I would want to hear my baby cry from the pain if being poked. It just seemed like she was gone, she just lay there, lifeless. I was a nervous wreck; I could do nothing but cry and pray. I felt so helpless, I just wanted to do something to help her, but all I could do is keep praying.

The lab results came back after about 30 minutes, and her ammonia had skyrocketed to over 700. This was devastating as normal range is between 30 and 70. I knew the risk of brain damage that comes from high ammonia. Even ammonia as high as 100 can cause lifelong brain damage, so I was terrified at what over 700 would do.

They admitted Sarahya to the PICU that night. They continued to give her IV fluids and TPN, which is nutrition through the veins rather than a feeding tube. They told me there was nothing left to do but wait. They explained to me that the chances of her waking up were slim, and if she did, there was still a risk that there was swelling on her brain, and she may not survive that. They also told me that even if she made a full recovery, she would likely be mentally handicapped, and may not be able to learn to walk or talk. I felt so helpless. I thought how could this be happening? This must be a terrible dream, it just can't be real.

I didn't sleep that night; I just sat there and prayed. I prayed so hard that I don't think I've ever been closer to God. I asked him to protect my

child, to bring her out of this safely. I sat and l held my baby's hand, and sang to her. She has always loved when I sing to her. I just knew she had to be in there somewhere. I just knew she would fight through. I reminded myself again that there was no place for tears here; there was only room for hope. I spoke to her and told her to keep fighting. I told her how much she was loved. I told her not to give up, and to come back to us.

The next day, family came to visit, and I had to explain everything the best that I could, over and over. I found myself reassuring everyone else that my child was a fighter, and she was going to survive. That day and the next, not much changed. She stayed unconscious, and I continued praying. On the fourth day, my mom arranged for the pastor at her church to come and anoint Sarahya and pray for her. Actually two different members of the church staff came that day, which I very much appreciated.

The elder who came and anointed her stayed for a while and comforted me. We had a long conversation about my feelings at the time. I revealed to him that I was having feelings of guilt that maybe my child was suffering as some sort of punishment for my past sins. I explained that although I had asked God for forgiveness, maybe I was not forgiven because I had been a hypocrite at times and continued to commit the same sins after I had asked for forgiveness. I could not wrap my mind around how I could truly be forgiven even though I am still a sinner. The elder then looked at me and said something that would change my life forever.

He pointed to my lifeless child and said "that is your child correct?" I said "yes." He said "is there anything in this world that she could do that you would not forgive her for?" I said "of course not, that is my child." Then he replied, "That is exactly the way our father feels about us." I just began to cry so hard, and I was so humbled, so thankful that my father, my God, loves me so much that I can be forgiven, even as the sinner I still am today. I still cry every time I think or talk about this, and I am crying now as I write it.

That day, my relationship with God became stronger than ever, and my faith became unwavering. Immediately after that, I was saved, right there in the PICU, next to my unconscious baby girl. I knew without a doubt that from then on, nothing could hurt my baby. I just knew that she would survive, and she would be just fine, because God would protect her.

The very next day, Sarahya began to wake up. It was a slow process; she was still very out of it at first. The doctors were still not very optimistic, and continued to remind me that she was still not out of the woods.

They expressed to me that although she was waking up; we had to wait a few more days to see how her brain would react. The days went by and she slowly became more and more alert. At about the 10th day, she was fully alert and showing many signs that her brain was working fine. In fact she even seemed to gain some skills that she did not have before the coma. For example immediately after waking up she was able to put her own Binky in her mouth, which she had never done before. After about a week and a half in the PICU, she was moved to a regular hospital room. She spent another week and a half in the hospital, and went home on her tube feeds and TPN.

The ER doctor and PICU doctors were at a loss for words. They came to visit her before she left the hospital, and told me they had no explanation for her recovery. They actually said it was miraculous. I felt so humbled and blessed, for doctors who have a scientific mindset to use the term miraculous was simply amazing. I knew that God had truly blessed me and performed a miracle in healing my baby.

The months went on and Sarahya had many, many more hospital admissions. I learned so much, I was not only a new mother, but I also became a great researcher, and nurse. I learned how to change TPN, as she was on TPN at home for seven months. Sarahya continued to get better and better. It was still slow progress, but I knew she would be ok.

She started therapy to help her catch up, as she was significantly behind in her development. She started physical therapy and occupational therapy when she was 16 months old. She began to sit up on her own at about 20 months of age. Then she began crawling shortly after that. She also began to eat by mouth around that time. After about six months of feeding therapy, Sarahya did not need her feeding tube anymore. Slow and steady wins the race they say, and Sarahya proved that.

A week before she turned 2 years old, Sarahya took her first steps alone! I don't think I've ever had a more proud moment in my life. They said my baby may never walk, but she achieved it. Over the next year Sarahya continued to get stronger and stronger. She began speech therapy to help her learn to speak, and continues to progress. She also began to show us her personality, and boy does she have personality! She loves attention, she loves praise, and she loves to perform!

My biggest fear out of everything was that my child would be mentally handicapped. I decided early on that I was not going to just accept the fact that she would be mentally handicapped. I decided that with enough work, with enough perseverance, she could overcome any obstacle, including any learning disabilities may have. So I began to work with Sarahya on things like body parts, shapes and colors, numbers, and her alphabet at a very early age. To my amazement, she caught right on. By the time she was 2 1/2 years old she knew her entire alphabet, she knew all her shapes and colors, she knew her body parts, and she could count to over 50. She amazes me every day.

Now Sarahya is 4 years old, and although I am biased, the smartest 4 year old I know. She can read over 100 words, she can spell her name, and she can count to over 100. She is learning some sign language now, and learning to speak some Spanish and Chinese! She just continues to learn new things every day, and she's like a beautiful sponge.

I know that God picked me for this challenging gift. I cannot wait to see what else she can accomplish through her strength and perseverance. She has taught me how to truly love, and never give up. She's also taught me how strong I really am and how strong and tiny little child can be. I feel so blessed to be her mommy!

God not only blessed me with Sarahya, but he blessed me with another child, Xayvior. Xayvior is 17 months old, and he also has MMA. Thankfully up to this point, Xayvior has not had near the complications that Sarahya had. He was born full-term, at 7 lbs. 11 oz. He was diagnosed with MMA through and amniocentesis while I was still pregnant. This was very helpful because we were able to treat him from the moment he was born. He has had a few hospital stays, spent some time in the NICU when he was born, and has some developmental problems, but overall has been very healthy. He also has a G button, and is just learning to eat by mouth. He does not sit up well on his own yet, or crawl, but he gets a lot of therapy for these issues. He is a little guy, which is typical of MMA children overall. He loves to watch his sister and I'm sure in no time will be playing and learning from her.

It can be discouraging at times, watching my son and realizing that he is smaller and developmentally delayed compared to other children his age, but I only need to take one look at my daughter and know that Xayvior will catch up too. I refuse to give up on either of my children. The same old pattern of one step forward and two steps back continues, but the ultimate goal remains the same.

MMA is commonly known as a popular sport in fighting. I am blessed to be the mother of two true MMA champions! My babies are in a fight for their lives, and they reign victorious through God's will!!

SONJA R., OMAHA, NE | MOTHER OF MMA CHAMPION, SARAHYA A. C., AND XAYVIOR S. S. | SSUNNYDAYZ4U@YAHOO.COM

Bronwen: Malonic Acidemia | Age 4½

It was the day I was scheduled to meet my little girl. Our whole family was filled with anticipation. She finally arrived at 12:15 on February 11, 2010. She was perfect. She had the most amazing dimples and big blue eyes. Her APGAR scores were great. After a day or so her pediatrician released us to go home. We could not wait to get home and begin our family of four. On the day we were to be released, the nurse on duty told us that we would not be leaving that day with our baby girl. All I remember thinking is why? Why? Why is she causing all this trouble and who is she, the nurse, to tell us we aren't going home. Can't she see that our baby is fine! I mean the pediatrician said so. I knew the shift change was coming and I was looking forward to it. After all, the next nurse wouldn't be so adamant. She'd let us leave with our baby girl. Little did I know the nurse going off duty informed the oncoming nurse that something wasn't quite right with our baby girl, who we had named Bronwen. The newly scheduled nurse told us the same thing. We would not be released that day and that she was going to do everything in her power to keep us there. This made me begin to evaluate. I did notice Bronwen wasn't nursing very well, but newborns usually don't. She was sleeping a lot, but newborns do that too, right? Whatever these nurses saw that no one else did I am so very thankful for them and their diligence in not letting us leave. They knew before anyone that something wasn't right. They were looking for any reason to keep us and that reason soon came. Bronwen's temperature dropped. It didn't drop much, but enough for them to get the NICU doctor involved. Bronwen was transferred immediately to the NICU, where they could monitor her and keep a close eye on her. Soon a geneticist was brought in. It was a whirl wind of tests upon tests. She was in the hospital a total of 13 days, which at that time seemed like an eternity, but now seems so long ago and so surreal. A meeting was scheduled with the geneticist where she sat us down and told us that Bronwen has Malonic Aciduria. She then told us there were only 25-30 cases reported worldwide, and that she had very little concrete information to give us. Many of the cases she had researched were severe, but that there was hope in catching it so early. She told us we would follow the same treatment as others with similar genetic disorders. We were put

through infant CPR training. Upon what we hoped would be Bronwen's last night in NICU, we were to stay in a room inside the hospital that was similar to a hotel room and make sure we were able to care for Bronwen properly. We would be waking every two hours to feed and record each feeding and medicine disbursement. Prior to leaving the hospital, we were told there was one more piece of information that they felt we must be told. One case had ended in infant death.

Fast forward 4 ½ years and we are raising a spunky, sassy, spirited, vivacious little girl. She loves to sing, dance, play sports, play with her toys and mostly fight with her brother. She remains healthy by sticking to a heart healthy diet, taking a MCT supplement, and daily doses of L-Carnitine. We certainly owe a lot to those two nurses and those who have fought so hard to get more tests in the newborn screening. I would like to say that once we got home and got caught up on our mail we did have the abnormal newborn screening results. It saddens my heart when I think of all the cases that could have been treated if caught early and again am thankful for those that have fought the fight to expand newborn screening. It certainly does save lives and nurses will forever hold a very special place in my heart!

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OAA EXHIBITS AT GMDI CONFERENCE IN DALLAS, TX - APRIL 2014

Flu season guide for patients with Inborn Errors of Metabolism

What is seasonal flu? Seasonal influenza or "the flu," is caused by influenza viruses, which infect the nose, throat, lungs. In contrast to other viral respiratory infections, such as the common cold caused by rhinovirus, the flu can result in severe illness with life--threatening complications.

When is flu season? Flu viruses circulate throughout the population all throughout the year. An increase above baseline flu activity occurs in the United States during the Fall and Winter and is known commonly as the "flu season." Flu activity usually peaks in January or February.

What are the symptoms of flu? • Fever or chills • Cough • Sore throat • Runny/stuffy nose • Muscle/body aches • Headaches • Tiredness

How does flu spread? People with flu can infect others up to 6 feet away. Flu viruses are spread mainly by droplets made when people with flu cough, sneeze or talk. A person might also get flu by touching a surface or object that has flu virus on it followed by touching their mouth or nose. Healthy adults are infectious starting 1 day before symptoms develop and up to 5 to 7 days after becoming sick.

Tips for flu prevention in patients with IEM:

Get vaccinated. This includes not only IEM patients but family members as well.

Avoid contact with sick people for at least 24 hours after the fever has gone.

Cover your mouth with a tissue when you cough or sneeze. Or you can cough or sneeze into their elbow.

Prevent the spread of germs. Avoid touching your eyes, nose and mouth.

Wash your hands with soap and water or a hand sanitizer.

Clean and disinfect surfaces and objects that may be contaminated by flu.

Why should individuals with IEM get vaccinated this season? In addition to the complications mentioned above that are associated with flu (e.g. pneumonia), patients with IEM have an additional concern. Many patients with IEM, including organic acidemias, fatty acid oxidation defects, urea cycle disorders and mitochondrial disease may experience an acute deterioration in their metabolic status during an infectious illness. This "acute decompensation" is due in part to the catabolic stress associated with illness. With fever, caloric needs are greatly increased. At times, these caloric needs may not be met due to decreased food/fluid intake, nausea and vomiting. To keep up with this increased need for calories during infection, body fuels including carbohydrate, fat and protein are utilized. For patients with IEM, this may lead to the build up of toxic metabolites or energy failure due to their enzyme deficiency.

How do flu vaccines work? Each year, Public Health Professionals need to predict which flu strains will be prominent in the coming flu season. These strains then form the basis for that season's flu shot. This vaccination causes the immune system to produce protective antibodies against the flu strains contained in the vaccination. It takes 2 weeks to develop these protective antibodies. Note: the flu shot does not protect against other respiratory viruses such as colds.

Why do patients with IEM need to get vaccinated for flu every year? A flu shot is needed every year due to the fact that flu viruses are constantly changing. New flu viruses may appear each year.

When is flu vaccine available? The CDC advises that people get vaccinated against influenza as soon as the vaccine becomes available. Influenza seasons can be unpredictable, and can even start as early as October. At the NIH Clinical Center, flu shots are available via the NIH MINI Study (see below), beginning in September.

How effective is the flu vaccine? In general, studies have supported that flu vaccination benefits public health, especially when the flu vaccine matches circulating flu viruses.

Do vaccines offer protection in patients with IEM? This is really an unanswered question. Since infections can trigger life--threatening acute metabolic crises in children and adults with IEM, we have decided to characterize the function of the immune system in patients with IEM. The standard of care for IEM patients is routine vaccination for influenza. However, there have been no studies to investigate whether the response to vaccination is normal in IEM patients. Vaccination represents a challenge to the immune system and can tell us how well it may be functioning. IEM patients may have enzyme deficiencies in their immune cells, a build--up of toxic metabolites, nutritional deficiencies, and energy deficiencies, all of which may impact immune system function.

The NIH MINI Study: Metabolism Infection and Immunity in Inborn Errors of Metabolism (*www.genome.gov/mini)* is an exciting study at the NIH Clinical Center (*clinicalcenter.nih.gov*). The main goal of our study is to learn about the function of the immune system in metabolic disorders. To learn whether you or your child develops immune protection to the flu vaccine or to learn more about your/your child's immune function, please contact us below. For more information about the study please visit our Web site: *www.genome.gov/MINI* or contact the study coordinator, Janet Shiffer, C--RNP by phone at (301) 451--9145 or by email at *ministudy@mail.nih.gov*.

Organic Acidemia Association

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