SEARCHING FOR A CURE HOPE FOR OUR CHILDREN

Propionic Acidemia Foundation

VOLUME 1, ISSUE 14 SPRING 2013

2013 PAF Education Conference
Saturday, June 29th
Denver, Colorado

DoubleTree by Hilton Hotel Denver-Stapleton North
4040 Quebec Street, Denver, CO
Hotel Reservations: 303-321-6666 Group Rate: $79+ tax (DO)
Say you are with Propionic Acidemia Foundation
RSVP by May 30th to get group rate.

For more info contact PAF: paf@pafoundation.com or 877-720-2192
Registration form on page 7.

Propionic Acidemia International Patient Registry Update

Launched September 2012, 31 people have completed the survey.

The Registries provide a way for PA patients and families worldwide to improve the understanding of the disorders and accelerate research by reporting information about how the disorder affects them. The Registry is itself an IRB-approved research project and the data collected will help characterize the condition of people living with PA. Please go to www.paregistry.org for more information and to begin the process.

PAF Awards Grants

$27,000 to Marisa Cotrina, Ph.D. University of Rochester, Rochester, NY. 2nd year continuation for her study on "The impact of PA on brain astrocytes: an in vitro model to test mitochondrial therapy in PA"

$21,200 to Loren Pena, MD, Ph.D. Duke University, Durham, North Carolina. New grant for her study titled "A prospective study of biochemical parameters reflective of metabolic control in PA". (See pg. 3)

INSIDE

MISSION: The Propionic Acidemia Foundation is dedicated to finding improved treatments and a cure for Propionic Acidemia by funding research and providing information and support to families and medical professionals.

VISION: To create a future where Propionic Acidemia can be prevented and any affected individual can be cured and live a productive life.

DO PEOPLE WITH ORGANIC ACIDEMIAS HAVE NORMAL IMMUNE FUNCTION

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VIRAL ILLNESSES AND IEM. Sometimes it starts with a fever, a sniffle, or a cough. Other symptoms such as nausea, vomiting and diarrhea may also occur. Different types of viral illnesses occur throughout the year whether during the cold winter months (e.g. influenza) or the hot days of summer (enteroviruses). Although many patients may weather these illnesses well, certain high-risk groups, such as patients with inborn errors of metabolism (IEM), are at greater risk for increased morbidity and mortality. Certain patients with IEM seem to take longer to clear infections, may become infected with unusual organisms, or may take a while to bounce back from their illnesses. Some of this may be attributed to their metabolic dysfunction, however, it should be noted that many IEM have been described as having some level of immunodeficiency.

THE IMMUNE SYSTEM AND INBORN ERRORS OF METABOLISM (IEM). IEM, especially organic acidemias (OAs), have been described as displaying deficiencies in immune function. For example, in OAs (e.g. methylmalonic aciduria, propionic acidemia, and isovaleric acidemia) reduced numbers of white blood cells and antibodies can be found. Since white blood cells and antibodies help the body fight off infection, patients with reductions in these critical components of the immune system may be at risk for serious infections. There are two likely mechanisms by which immune dysfunction may occur in IEM. First, enzymes deficient in IEM may also be deficient in immune cells. This may lead to a block in metabolism that is critical for immune system function. Second, toxic metabolites may build up and have damaging effects on immune system function. Toxic metabolites such as lactic acid and ammonia are known to inhibit the function of immune cells. While there are at least 13 IEM that have been identified as having some form of immunodeficiency, the scope and depth of the problem is under-characterized.

NUTRITION AND THE IMMUNE SYSTEM. The management of IEM oftentimes involves restriction of offending dietary components, such as protein, which may lead to nutritional deficiencies. Patients may display biochemical (e.g. decreased prealbumin) and physical signs of malnutrition (e.g. hair loss, poor growth). Nutrient and vitamin deficiencies may also coexist. A recent review of patients with phenylketonuria, an amino acid disorder, described suboptimal nutritional outcomes following treatment.[1] Besides growth impairment, deficiencies in vitamins (B6 and B12), micronutrients (iron, zinc), essential fatty acids, and protein intake (decreased bone mass and density) were described. These nutritional deficiencies may affect immune system function.

Deficiencies in energy status, protein, vitamins and nutrients, alone or in combination, can lead to clinically significant immunodeficiencies. Nutritional deficiencies at critical periods of maturation of the immune system may hamper its development leading to an immunodeficiency.[2,3] In addition to immune system development, proper nutrition is also critical for maintenance of the immune system. For example, deficiencies in various nutrients including protein, zinc, iron, vitamin A, arginine, citrulline and glutamine may affect white blood cell function. The adequacy of nutrition and immune function is highlighted in elderly populations. Elderly patients often have numerous nutritional deficiencies, which may affect their ability to produce protective antibodies after the flu shot. This reduced vaccine efficacy may be overcome by nutritional supplementation and optimization.[4-6] These and numerous other studies suggest that proper nutrition is essential for immune system function.

THE NIH MINI STUDY: METABOLISM, INFECTION AND IMMUNITY. Since infections can trigger life-threatening acute metabolic crises in children and adults with IEM, especially in those with OAs, 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 childhood and seasonal illnesses. However, there have been no studies to investigate whether the response to childhood and seasonal vaccination is normal in OA 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 and nutritional 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 new 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, especially OAs.

There are two ways to participate:

1) Travel to the NIH Clinical Center in Bethesda, Maryland for an evaluation. Travel costs will be provided for patients and their families. Additional visits may be suggested dependent upon the level of subject participation. The visits will typically be 2-3 days long. At the first visit, we will perform a physical exam and do a detailed nutritional and immunologic (continued on page 6)

BIOCHEMICAL PARAMETERS & METABOLIC CONTROL IN PA

Loren Pena, MD, Ph.D

Propionic acidemia (PA) was initially described five decades ago, yet our current understanding of the disorder's natural history, pathophysiology, and goals for treatment is limited. Current treatment recommendations are based on clinical opinion, as there is a lack of studies on which to base standards of care (Sutton et al. 2012; Chapman et al. 2012). There is also a limited understanding of biochemical parameters that may reflect appropriate metabolic control. Prospective studies are therefore crucial to extend our current understanding of the pathophysiology of complications and the goals for therapy.

Current practice for medical and dietary management of PA includes monitoring of growth parameters, carnitine supplementation, and amino acid levels. A previous publication compared plasma propionate concentration in the fasting and fed state in a small number of individuals with PA (Sbai et al. 1994). Results indicate, not surprisingly, that plasma propionate levels increase in the fasting state. Likewise, a comparison of odd-numbered long chain fatty acids between unaffected controls and individuals with PA observed a chronic elevation in PA, with acute increases during metabolic decompensation (Meissner et al. 2004).

The current limitations to our understanding of the disorder and goals for management present barriers to treatment. This impacts patient care, as treatment goals and health care supervision are specific to the practitioner's experience. Prospective studies, with specific intervals and parameters for surveillance, would improve our ability to care for individuals with PA by providing objective criteria for metabolic control.

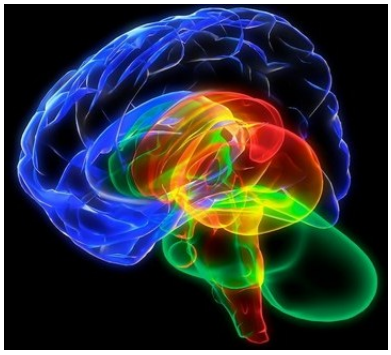
The rationale for this study is to establish laboratory correlates for metabolic control that may aid in disease management. As part of this study, we will investigate whether specific biochemical parameters, such as C3 acylcarnitine, plasma glycine, and urine citrate-to-methylcitrate, correlate with metabolic status in individuals with PA. We will also explore whether risk factors for pancreatitis can be identified in the cohort. This study will be performed in collaboration with investigators at Lurie Children's Hospital of Chicago, University of Illinois at Chicago, and Carolinas Medical Center, and will be valuable in exploring whether specific biomarkers can guide disease man-

NEUROIMAGING IN PROPIONIC ACIDEMIA

Andrea Gropman, M.D.

This grant uses non invasive multimodal neuro imaging in the investigation of neuronal injury in patients with Propionic acidemia (PA). Key scientific personnel who will provide expertise to this project are the P.I., Dr. Andrea Gropman, who is a pediatric neurologist and geneticist and who has experience in the use of multimodal neuroimaging in the study of inborn errors of metabolism. Dr. Stanley Fricke is the physicist who has been instrumental in the design of special imaging sequences, and Dr. John VanMeter is the director of the Center for Functional and Molecular imaging at Georgetown University.

This year, 4 patients were screened as potential subjects, however, three were found not to be suitable for the study due to cognitive and/or medical exclusions. A fourth subject, an adult was eligible, however, did not re-contact the PI regarding potential dates for the study.
Because no subjects were imaged, the PI is requesting a no cost extension to the grant and the help of the PA foundation to identify 6-8 suitable subjects who can complete this study.



Publication Note: The PAF Newsletter *is published twice a year. Readers may subscribe by writing to PAF, registering online or calling 877-720-2192. Letters and article submissions are welcome for consideration and may be sent to paf@pafoundation.com or mailed to Propionic Acidemia Foundation 1963 McCraren, Highland Park, IL 60035. If you would like to be removed from our mailing list or receive the newsletter via email, please contact us. We are deeply appreciative to Publishers Printing Company for donating the printing costs of the newsletter.*

REUBEN'S STORY

By Adrianna Kleckley

When people ask me about my brother it's impossible NOT to smile. He is such an amazing person! He's friendly, strong, funny and has an infectious laugh. Reuben is completely comfortable being himself. He doesn't judge others and has the purest soul I've ever met. It doesn't bother me that he can't drive, that sometimes I have to "translate" what he's saying to others, or that **everything** in his world is related to a sport's team- that's "Rube", my baby brother and my best friend.

I remember the day he was born very clearly, I was five years old and I was nervous, very anxious to meet what I thought would be a little sister. I remember being ushered into the room with my grandparents and my mama had the bow on the newborn cap covered up with her hand and then FINALLY she unveiled it and my life was forever changed- Reuben Wade Kleckley was born March 22nd, 1984. He was named after four generations of Kleckley men and I'm sure my parents had dreams of him playing professional baseball like my daddy and granddaddy did, but God had bigger plans for him.

When Reuben was two days old, he became very ill. He was having seizures and went into a coma- and the doctors really couldn't tell my parents why this was happening or what was wrong. No one had any answers and I remember it was a very confusing time for me because what was a happy occasion quickly became a scary time for our family. Once he was moved to ICU, I wasn't allowed to see him because no children were allowed, and that was hard because as a new big sister that's all I wanted to do. After a few days, the nurses and my mom got together and broke the rules- dressing me in scrubs from head to toe so that I could hold him. I remember his baptism and watching him being baptized in ICU with my baptismal gown on, wires all over and a specimen cup taped to side of his head so he wouldn't pull out his IV again- he was such a pitiful little sight. When Reuben was about a week old, he was flown to Johns Hopkins in Baltimore and was diagnosed with Propionic Acidemia, at the time there were only about 75 cases in the country so the doctors really didn't give my parents a lot of hope. Most children didn't live past infancy and those who did, typically had significant developmental delays. The latter proved true for Reuben.

As a child, in those first years I don't think I really noticed that he had global delays- not walking until he was two or using phrases until he was four. It never dawned on me that he wasn't doing things like other toddlers, I was just happy he was with us since there were so many times he almost wasn't. I think we were more focused on his health with surgeries and trips to Duke to see specialists than any delays. I know my parents knew early on that he was going to have challenges, but it took me awhile before I noticed he was different. I remember the questions from friends and family and sometimes the stares when we would go out in public- it made me angry as a child, but it never made me angry at Reuben, it made me angry at the ignorance or other people. The only thing that bothered me about growing up with a special needs brother was that it was very isolating, I didn't know anyone else like me and I didn't have any friends who understood. I had no one to talk to about it. My parents would try, but I was afraid of feeling or saying anything that might hurt them or make them worry.

I think the question I get asked most often is, "Do you ever wish your brother was normal?" Sometimes people are shocked when I say "no". I mean, what is "normal"? I think about how happy Reuben is, how much he enjoys the simple things in life and how, at 28, he is completely unaware of the negativity in this world. He's had a lot of struggles, but he's had so many more positive experiences! Having a sibling with special needs is not something you wish for and it's not always easy, but Reuben has given us so much more than we could ever hope to give him. Christmas mornings are still exciting, watching him sing "Victory in Jesus" always brings tears to my eyes and it's because of him that I've dedicated my professional career to working with children with special needs.

For a long time I'd heard "you're so good with Reuben"… so, my family wasn't surprised when I changed majors my junior year at USC, to work with children with disabilities. Once I met my first child with autism, I was officially hooked. I became an Early Interventionist after graduating in 2003 and in November, 2011, I partnered with a colleague to form Carolina Behavior & Beyond. Our company provides early intervention services to children with disabilities and developmental delays, mainly serving children from birth to age five. I love what I do and it's truly amazing to see a child develop and transform before my very eyes. I found my purpose in life and I know without a doubt, I have Reuben to thank for that. He's taught me that being different is not the end of the world, that there is wealth in every life if you have the heart to find it, and that you don't have to be in the big leagues to pitch a no-hitter.

PA ENERGY DEFICIENCY UPDATE

By Kimberly A. Chapman

Individuals with Propionic acidemia (PA) can have symptoms that are reminiscent of energy deficiency disorder like oxidative phosphorylation disorders. These symptoms include metabolic stroke-like episodes, myopathies, cardiomyopathies and optic neuropathies. Our laboratory is trying to understand these findings.

We are starting a study that looks at resting metabolic rate (RMR, the amount of energy one needs when at rest) in individuals with PA (and related disorders) when they are sick and when they are healthy to determine whether RMR changes with illness in PA and whether this is similar to findings in individuals without these disorders. Presently (due to the importance of measurements in individuals when they are sick), we are doing this at our own institution, if results are promising we will try to expand to other clinics. Preliminary data are promising.

We are also looking at cell lines from people with PA to determine whether we can identify why individuals with PA have these energy deficiency symptoms. We are presently examining whether the Kreb cycle enzymes in lines from PA individuals work like and are at the levels seen in sex and age-matched control cell lines. We are doing this because propionyl CoA is a precursor to succinyl CoA and so important to maintaining the health of the Kreb cycle. Preliminary studies show different amounts of several of these enzymes between control lines and those from PA individuals. Enzyme activity assays are about to begin for these same lines.

Thank you to all who made these studies possible, those who have donate money and especially those who donated their or their loved one's cells for research

Coriell Institute for Medical Research: PA repository update

There are currently 52 subjects available in our online catalog. We have shipped 92 cell cultures and 50 DNA samples to researchers. We have not received a submission of Propionic Acidemia since 2008, and would love to receive some new submissions. The repository can receive blood or fibroblast lines made from skin biopsies.

ORGANIC ACIDEMIAS & IMMUNE FUNCTION (CONT')

assessment for all study participants. We will offer Hepatitis A vaccination, which is part of the current Pediatric Vaccination Schedule (http://www2.aap.org/immunization/IZSchedule.html).

These recommendations are relatively recent, coming in 2005, and many children over the age of 8 years may have missed getting vaccinated against Hepatitis A. Therefore, you or your child would potentially benefit from receiving this vaccine. During "flu" season, the influenza vaccine is recommended for all children with chronic illness, including those with OAs, and will also be offered. As part of the assessment, we will measure whether or not you or your child's immune system was able to respond appropriately to vaccine(s). This includes vaccines that are offered as part of the study as well as past vaccines received during childhood.

Additional tests may include:

- body composition testing, including a DEXA scan
- energy expenditure testing

*2) **Donate blood and tissue samples to the study.*** For individuals who are unable to travel to the NIH Clinical Center, blood and tissue samples may be donated to the study. Tissues of interest include: ***fibroblasts from skin biopsies, and materials acquired from other medical procedures including lymph nodes, tonsils, spleen, and especially cord blood.*** The acquisition of these samples will be coordinated with your local medical provider(s).

The NIH MINI team is available to discuss eligibility for this protocol with anyone that may be interested in participating and welcomes all inquiries.

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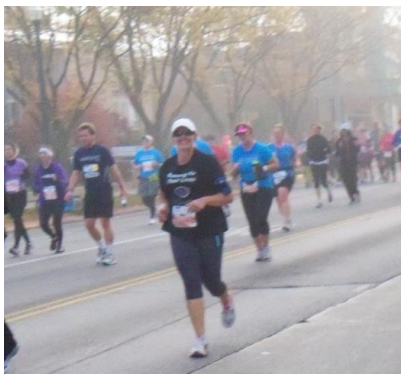
PAF FUNDRAISING SPOTLIGHT

PAST EVENTS AND CAMPAIGNS



- 10/21/12 **Tara Gerlach, Columbus Half Marathon** (OH), raised $585 (top right)
- 11/18/12 **Brittany Smith, Big Sur Half Marathon** (CA), raised $648 (middle right)
- 12/8/2012 **Kalanityam and Indian-Fusion Dance Academy, Jhalak Dreams**, San Jose, CA, raised $1500!
- 2/3/2013 **Young Family Superbowl Party**, King of Prussia, PA, raised $1030! Years of Success! We would like to thank everyone who participated in this year's Superbowl pool for the Propionic Acidemia Foundation. It was easy with the support of our friends and family and fun to do!
- 2/3/2013 **Branch Family Superbowl Party**, Kokomo, IN, raised $1080!
- 2/18/2013 **Crop for PA Scrapbook Event**, Lewis Center, OH, raised $1800 (bottom)
- 2/19/2013 **TGBK Shootout**, Deerfield, IL, raised $1500 and counting! (bottom right)

UPCOMING & ONGOING EVENTS AND CAMPAIGNS

- 9/14/2013 **8th Annual Tailgate Party & Corn Hole Tournament**, Gahanna, OH, GwenForACure.com
- Join the PAF Pounding the Pavement for PA team or start your own! Run in any race, around your block, or become a "virtual runner" Contact Brittany Smith for more information at paf@pafoundation.com or 877-720-2192

Fundraise online by doing what you already do!

- Online through GoodSearch.com, GoodBuy.com, GoodDining.com, GoodShop.com: $1391donations
- Search or shop through iGive.com: iGive donations, $3666
- Sign up for eScrip at http://escrip.com/
- Sell items on Ebay using MissionFish. Pick what % goes to PAF!

We want to hear from you! Have a PA story to tell, event to promote or news? Spring newsletter submissions due by July 31!

PAF Education Conference Registration Form

Saturday, June 29, 2013
DoubleTree by Hilton
4040 Quebec ST, Denver, CO 80216

Please complete the form and email to paf@pafoundation.com or mail to 1963 McCraren, Highland Park, IL 60035:

1. **Personal Information**
   Name: _____
   Address: _____ City_____ St: _____ Zip _____
   Email Address:_____ Phone: _____

2. **Names of children attending with you:**
   a. Child's Name: _____ Age:_____
   PA? ☐Yes ☐No Low protein meal needed? ☐Yes ☐No
   Allergies? ☐Yes ☐No If yes, specify: Attending Child Care? ☐Yes ☐No
   b. Child's Name: _____ Age:_____
   PA? ☐Yes ☐No Low protein meal needed? ☐Yes ☐No
   Allergies? ☐Yes ☐No If yes, specify: Attending Child Care? ☐Yes ☐No
   c. Child's Name: _____ Age:_____
   PA? ☐Yes ☐No Low protein meal needed? ☐Yes ☐No
   Allergies? ☐Yes ☐No If yes, specify: Attending Child Care? ☐Yes ☐No
   d. Child's Name: _____ Age:_____
   PA? ☐Yes ☐No Low protein meal needed? ☐Yes ☐No
   Allergies? ☐Yes ☐No If yes, specify: Attending Child Care? ☐Yes ☐No

3. **Others attending:**
   a. Name: _____ Relationship: _____
   b. Name: _____ Relationship: _____
   c. Name: _____ Relationship: _____

4. **Total number attending:** _____

5. **Is this your first PAF event?** ☐Yes ☐No

6. **Are you a professional or vendor attendee?** ☐Yes ☐No

There is no charge for families with a PA affected member to attend.
Please contact us for space availability for non-family registration.

Thank you and we look forward to seeing you at the conference!

Please do not bring any foods containing nut or peanut because of allergy concerns.

Pictures of the Doubletree by Hilton Hotel Denver-Stapleton North

Sharing and networking prior to a session at a previous PA educational conference

Help Us Find the Cure!

*Name*_____ *Please send an acknowledgement to:*

*Address*_____ *Name*_____

City, State, Zip _____ *Address*_____

*Phone*_____ *City, State, Zip*_____

*E-mail*_____

*Enclosed is my contribution of $*_____ *in honor of/in memory of* _____

If you work for a company that has a matching program, please include the matching form.

Please mail your check made payable to: Propionic Acidemia Foundation 1963 McCraren, Highland Park, IL 60035

Thank you for making a difference.

SEARCHING FOR A CURE
HOPE FOR OUR CHILDREN

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