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MSUD NEWSLETTER

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BIRTH ANNOUNCEMENT

KAYLA DIANE DEGAETANO

Born January 10, 2013

By Katelyn DeGaetano, Classic MSUD age 30

My husband Peter DeGaetano and I are proud to announce the birth of our daughter, Kayla Diane, a healthy baby girl. Because my husband is not a carrier of the disease, Kayla does not have MSUD. I had a very healthy pregnancy with no complications. My metabolic doctor Dr. Levy and his team at Children's Hospital in Boston worked collaboratively with the staff at the Brigham and Women's Hospital where I delivered to implement a birth plan that was intricately designed by Dr. Levy and his team. It was determined that they would induce labor in order to ensure that all doctors, staff, and medications were in place at the

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A Silver Lining…

By David Fischler

Classic MSUD age 25

Fortunately, much has changed in the past 25 years and the diagnosis of maple syrup urine disease is handled and not construed as the end of the world. When I was born in 1988, the diagnosis of MSUD (if diagnosis took place at all) signified the beginning of an impeccably scripted horror story that was about to begin. In general there was lack of knowledge by virtually every doctor you would come across and utter frustration (mentally, physically, and even financially) for both the parents and child. I was one of the lucky ones. I was diagnosed at 16 days old and was treated just in time leading to no permanent damage, but it was not easy on my parents. As I look back on it, it was a nightmare for them those first few days, weeks, and years as they tried to pay for my medications and keep me healthy. As rough as it was they persevered and I survived.

By the time I reached the seventh grade, I was curious about "what was wrong with me." I knew I was not allowed to eat any pizza or hamburgers, and I had been in and out of hospitals.

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time of delivery. I was induced gradually over a forty eight hour period; however, when I did not progress, I had a c-section. This major surgery also did not cause any complications with my MSUD. Rather than having my leucine levels sky rocket, which was a possibility, my levels dropped too low. I was monitored in the hospital for approximately three weeks and we adjusted my diet as necessary. I was given a peripheral line of TPN (calories without protein) throughout my hospitalization, which we believe helped stabilize my levels. At this point and even now, a high calorie count is equally important as moderating my protein intake.

During my pregnancy, my tolerance for protein increased immensely. I went from a 10-12 gram limit to approximately 40 grams per day. When I was discharged, I was on a diet of 20 grams per day because Kayla was breastfeeding. I never thought that this would have been an option because of my limited diet; however, my milk was tested for protein and it contained more protein than that of other women. Kayla has had to be monitored more closely for height and weight to make sure that she is growing at an appropriate rate and she has grown and developed wonderfully. She will be eight months soon and I am still breastfeeding 2-3 times per day. Pregnancy and delivery were not complicated for me as a patient with MSUD, but breastfeeding has been a challenge due to the necessity for balance. If Kayla's feeding schedule is even the slightest bit off, then I need to adjust my protein intake. For this reason, my leucine level was elevated a couple of times since I have come home. At times, it has been a challenge, but the bond and the benefits for the baby are well worth the work.

Throughout my pregnancy and delivery, I referred to the numerous doctors at Children's and the Brigham as "The Dream Team." I have always known that I wanted a family- it was my dream, and without this group of dedicated people I would never have had the courage to make this happen. I owe all of this to Dr. Harvey Levy who first made me believe that it was possible to have a healthy pregnancy and then took me through every step and created a team that worked together to make this happen. Fortunately, Dr. Sameer Chopra worked at both the Children's Hospital and Brigham and Women's, so he coordinated both teams. My OB/GYN, Dr. Louise Wilkins-Haug, has a background in genetics and a familiarity with MSUD and Dr. Levy. Each day the amazing nurses and doctors at the Brigham met with the Children's team to discuss my progress. My husband and I are eternally grateful for the care that I received. We told the team that we would be back. ■

A Few Words From the Editor

Karen Dolins, EdD, RD, CDN
Newsletter Editor

This issue of our newsletter opens with articles written by 2 adults with MSUD who have achieved milestones that would have been unheard of a few short decades ago. Katelyn DeGaetano (classic MSUD, age 30) announces the birth of her daughter Kayla. She tells of her experience maintaining her health as well as her baby's throughout her pregnancy, and treats us to pictures of her gorgeous girl. David Fischler (classic MSUD, age 25) tells us of his academic success and the path which has led him to pursue a PhD in analytical chemistry.

We continue to include the latest research which we hope will one day lead to a cure for MSUD, and we include recipes and other information to help us manage our lives healthfully until that time. I am grateful to all who contribute, from our own members with their inspiring stories to the researchers who keep us up to date on their important work. Please continue to keep us informed of any milestones: births, academic and sports accomplishments, graduations, religious milestones, weddings, and anything else that is important in your life. If you have suggestions for subjects you would like to see covered, please let me know. It takes us all to keep our organization strong.

I can be reached at krdhed@aol.com or 914 391 2982.

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However, I still knew little more than that. That spring, my biology teacher assigned open topic research papers. Mine…was MSUD. I began reading and learning and for the first time I had an idea about MSUD. I can honestly say I appreciated understanding a great amount of the details that seemed unclear at the time. I now may have even known more than my parents. However, the true benefits would come from the research itself. Until then I viewed science as just another class that was pretty easy, and I was pretty good in it. The class I had really enjoyed was math. However, following that project I developed a passion for science, in particular the biology and the chemistry. Fast forward 18 years, and I have graduated from the Georgia Institute of Technology with a degree in Biochemistry with honors, and am currently pursuing a PhD in the field of analytical chemistry at The University of Georgia.

Yes, being born with MSUD is difficult for all those involved. It is difficult road, but in my case it also shaped who I became. That day in seventh grade, if I had not found a project that inspired me…who knows? I may have been a mathematician today. Life with MSUD has led me to this. So, as tough as it may be, MSUD is a part of me in more ways than just a disease. So, as tough as it may be, just remember: Keep looking. Every cloud has a silver lining…I have found mine. ■

Do People With Inborn Errors of Metabolism (IEM) 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 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 IEM. IEM have been described as displaying deficiencies in immune function. For example, in organic acidemias 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 (e.g. branched chain keto acid dehydrogenase in Maple Syrup Urine Disease (MSUD)). 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, ammonia, and the organic acids seen in MSUD, 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 decreasing 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, leucine, 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, 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 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, 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

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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. The NIH MINI team is available to discuss eligibility for this protocol with anyone that may be interested in participating and welcomes all inquiries (2 years of age through adult).

For more information about the study please visit our Web site:
http://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. ■

Save the Date:
MSUD Symposium 2014
July 24th - July 26th
at the Embassy Suites
Columbus Airport
Columbus, Ohio.
Plan ahead to attend!

References

1. Enns GM, Koch R, Brumm V, Blakely E, Suter R, Jurecki E. Suboptimal outcomes in patients with PKU treated early with diet alone: revisiting the evidence. *Mol Genet Metab*. Oct-Nov 2010;101(2-3):99-109.
2. Keusch GT. The history of nutrition: malnutrition, infection and immunity. *J Nutr.* Jan 2003;133(1):336S-340S.
3. McDade TW, Beck MA, Kuzawa C, Adair LS. Prenatal undernutrition, postnatal environments, and antibody response to vaccination in adolescence. *Am J Clin Nutr.* Oct 2001;74(4):543-548.
4. Girodon F, Galan P, Monget AL, et al. Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients: a randomized controlled trial. MIN. VIT. AOX. geriatric network. *Arch Intern Med.* Apr 12 1999;159(7):748-754.
5. Chavance M, Herbeth B, Mikstacki T, Fournier C, Vernhes G, Janot C. Nutritional support improves antibody response to influenza virus vaccine in the elderly. *Br Med J (Clin Res Ed).* Nov 9 1985;291(6505):1348-1349.
6. Wouters-Wesseling W, Rozendaal M, Snijder M, et al. Effect of a complete nutritional supplement on antibody response to influenza vaccine in elderly people. *J Gerontol A Biol Sci Med Sci.* Sep 2002;57(9):M563-566.

Adipose Tissue Transplantation for Treatment of MSUD

By Christopher Lynch, PhD
Penn State College of Medicine

Patients with MSUD can be in danger of experiencing elevations of their branched chain amino and keto acids (BCAAs and BCKAs), even when carefully monitoring their diet, due to every day stress or infections. As our body responds by mobilizing fuel including amino acids from muscle (protein breakdown), an unpredictable back up of BCAAs and BCKAs may lead to the unpredictable metabolic crises that parents are familiar with.

A recent advance in the treatment of MSUD helps with this problem and helps those with MSUD eat more normal diets. Most readers will know that this new treatment is liver transplantation, which has been spearheaded and pioneered by doctors including Drs. Strauss and Morton at the Children for Special Children. Liver transplantation provides sufficient metabolic capacity for many patients to resume a normal diet. Their results so far have been very exciting. However, there is currently a shortage of donor livers worldwide and the cost is estimated to be upwards of $500,000 during the first year of treatment according to some organizations (http://www.transplantliving.org/before-the-transplant/financing-a-transplant/the-costs/), creating potential barriers.

A recent paper from our group (http://www.ncbi.nlm.nih.gov/pubmed/23800641) published in the journal, Molecular Genetics and Metabolism, showed that adipose tissue transplantation could have promise for MSUD treatment. We studied different modes of transplantation in two different mouse models, the BCATm (BCAT2) and PP2Cm (PPm1K, MSUDMV) gene knockout mice. After surgery, 51-81% decreases in BCAAs were observed and alloisoleucine was also significantly decreased. You may not have heard of fat transplantation before or think it sounds far fetched, but this procedure is being performed every day by reconstructive surgeons for breast and other reconstructive surgery across the country. Actually a whole industry has grown up around this procedure with new patents and FDA approvals coming every year. For example, a company called Cytori has had recent FDA approvals for devices to process and remove contaminants from the fat prior to transplant and to harvest regenerative stem cells from fat. Other companies have competing devices for removing contaminants and re-injecting the fat including specialized surgical equipment.

Our idea to try this approach came from two recent studies where we found that fat had previously unrealized stores of the branch chain amino acid metabolizing enzymes in humans and rodent models.

We are now trying to improve on the results we recently published. We are learning from plastic surgeons how to best transplant the fat to help blood vessels develop through the fat. That should help circulate more amino acids through the transplanted tissue. We also hope to study adding regenerative cells derived from fat (ADRCs) along with the transplanted fat to help preserve it in the long term. ADRCs may not only replenish the fat, but also help reduce rejection as they do when transplanted elsewhere.

Presently fat grafting involves moving fat from one location to another in the same person for reconstructive or plastic surgery. But for MSUD, as is the case for liver transplant, the transplant would have to be provided by donors to provide the missing enzymes. That means transplant drugs would be needed as in liver transplant. But for every kind of organ transplant, a different protocol and cocktail of drugs is used and nothing is known about how to prevent fat rejection. Therefore another goal moving forward is for us to investigate the current arsenal of drugs and identify those most compatible with adipose tissue transplantation. In addition we are planning proof of concept studies in which human fat will be grafted into a version of our mouse model of MSUD that will be able to accept human tissues.

If this continues to go well, we believe it may be easier to get fat donors compared to other organs and that fat transplant operations would be far less expensive than other kinds of transplants. An alternative outcome could be the use of fat transplant as a bridging therapy before liver transplant.
This research was conducted by a team including Dr. Heather Zimmerman, a veterinary researcher and surgeon and two molecular biologists and biochemists, Dr. Kristine Olson, and Dr. Gang Chen, all of Penn State College of Medicine.
The research was funded by a grant from NIH, NIDDK through a grant mechanism that provides limited funds for high risk/potentially high gain research. We are now submitting proposals to continue this project. ■

ASSISTANCE AVAILABLE FOR 2014 SYMPOSIUM

The United Services Foundation kindly promised once again to donate funds for the purpose of helping families with the expenses of attending the 2014 Symposium. This fund is intended for families or persons who would otherwise not be able to afford the travel and/or hotel expenses. Those who have never attended an MSUD Symposium will be given priority. Funds are limited so we want to know as soon as possible if you are interested. For those outside the USA, it is important to get the process of passports and visas started at the beginning of the year. Late applications do not allow enough time to obtain visas and make airline reservations. We wish to make it possible for all interested families to attend.

For information contact Wayne and Joyce Brubacher at 574-862-2992 or e-mail: wjbrubacher@afo.net.

DIETARY ADHERENCE IN MSUD

Anita MacDonald
Consultant Dietitian in Inherited Metabolic Disorders, Birmingham Children's Hospital, UK

Introduction

The treatment of maple syrup urine disease (MSUD) necessitates a life-long diet. It aims to reduce intake of the branched-chain amino acids while maintaining normal growth and nutritional status, and minimising metabolic decompensation. The anxiety and pressures experienced by patients and their families in adhering to dietary management has received limited study. The primary aim of this report is to highlight the hurdles that need to be overcome in gaining dietary adherence in MSUD at various ages.

Adherence

In non-MSUD amino acids disorders treated by diet (e.g. PKU), it is known that blood control of the offending amino acid deteriorates with age, especially from around 10 years of age. Although data is more limited in MSUD, evidence would suggest a similar pattern. Two European MSUD studies reported on adolescents and adult patients who maintained average leucine concentrations higher than the usual treatment range (1, 2). Therefore, it is clear that maintaining strict dietary adherence throughout older life is challenging.

The Burden of the Disorder and Dietary Management

The need to adhere every day to strict dietary management is relentless. Treatment is not only about a rigorous dietary regimen, but an endless sequence of administering medical food, home blood tests, emergency procedures, and numerous visits to hospital to see professionals, and this experience is shared by the entire family. Children may have physical or behavioral feeding difficulties or have limited appetites, and may require constant coercion to take their medical food three to four times daily, which is exhausting for parents. It is likely to have disruptive effects on the family lifestyle, limit time spent on non-MSUD children (3), and participation in normal activities such as holidays may be affected. Any accompanying physical or neurodevelopmental disability will create additional challenges. In addition, it is not unusual to have more than one child with MSUD thereby increasing the family workload. In PKU, it was reported that the median time burden associated with management was 527h/year (1 h and 24 min/day) for parents and 175h/year (30 min/day) for adult patients(4). This time is likely to be higher in MSUD.

The Patient's Family Characteristics

Overall outcome in children depends on parental ability, their discipline, motivation, organization skills, and overall coping ability to continually apply and supervise the dietary regimens. Emotional stress has been reported in 78.4% of MSUD parents(3), and differences in parenting styles may be a source of marital conflict(5). It has been shown in other conditions(6)that feeling emotionally depleted can compromise parent's ability to respond to acute illness, and this may be analogous for MSUD. Family circumstance has the potential to either support or derail adherence to dietary treatment. Households headed by one parent have increased in some countries and low family cohesion and divorce has been shown to have a negative impact on adherence in similar conditions(7). Family disengagement and criticism may be associated with poor adherence in children.

The Patient Responsibility

As children mature, they are expected to take more responsibility for their diet therapy, and gain more practical and theoretical knowledge so they can lead independent adult lives. This may be particularly challenging for patients with low education ability(5). In particular in MSUD, poor planning, limited organizational skills and poor attention may affect the ability to self-manage their diet outside the home.

In teenagers, some adherence issues surround the need to be accepted by peers and the need to fit in. They may lack awareness about the effects poor adherence has on some aspects of treatment. Also the diet is seen to complicate social relationships when it makes their condition visible. Teenagers may be less willing to take medical formula in front of others. Negative school experiences have been reported in MSUD(3).

Cultural and Religious Influences

MSUD is more frequent in populations with a high level of consanguinity, and is particularly prevalent in Muslim communities living in western countries but originating from South Asia and the Middle East. Structural and practical constraints include living in poor housing with limited cooking facilities, large sized families, illiteracy and/or poor language skills; the latter is a major barrier to understanding and accessing basic information about the dietary treatments, which affects their ability to adhere to treatment.

Adherence and Information Sources

Parents encounter an overwhelming amount of unrestricted and unchecked information from websites, Facebook, Twitter and other sources. MSUD specific information is sparse.* Equally, patient associations are well established for PKU, but in European countries due to the infrequent incidence of MSUD, family support is less available. Furthermore, families may receive care from a non metabolic-specialist health professional care team who may lack the

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necessary experience to support and enable the family to deliver the optimum treatment, which may lead to conflict between parents, patients and clinician.

Adherence with Medical Food

Although medical food is an essential part of treatment, due to its taste adherence is a major issue (3, 5, 8). The development of MSUD specific medical foods has always lagged behind that of the more common disorder, PKU, as international demand is more limited. Consequently the range and flavors available for MSUD medical foods is limited, which may add to dietary non- adherence. Fortunately newer, innovative products are now available which may improve this situation (8).

Financial aspects

Although internationally there is a wide range of special low protein foods available, many governments expect families to purchase them, creating a high annual financial burden (4). Additionally the cost burden of transportation to clinics and blood testing affect the ability to adhere to diet.

Conclusions

In MSUD, dietary adherence is challenging and affected by many complex interrelated factors. The production of international web based educational tools is likely to be significant in supporting patients and caregivers. There is much to be learnt by community studies observing day to day issues in patient management in order to improve practical advice and support in the future.

Practical Recommendations

Medical Food

• Establish a time routine for medical food: always give at the same time each day. Ensure it is always completed.

• An adult should always supervise the medical food intake in children (at home, nursery or school).

• Try and always keep at least one months supply of medical food in stock.

Education and Support for Children, Teenagers and Adults with MSUD

• Encourage children to play at 'cooking' with their foods from an early age e.g. they can decorate low protein biscuits, cake pops and low protein biscuits. All of this helps to create an interest in food and their diet.

• By the time a child is attending school it is important they have some knowledge about their condition. They need on-going education about the foods they can and cannot eat, why they take their medical food and the need for blood tests. Give them plenty of 'hands-on' activities. Children can plan meals, shop for food, measure ingredients, and prepare meals and snacks. Keep all activities highly interactive, creative, and fun.

• Consider the use of 'role model' peer support, peer support groups, suitable and 'monitored' face book or internet chat lines to help teenagers with MSUD.

• Consider attendance at 'supported' summer camps for adolescents and adults to share and discuss issues that concern them. Attendance at group practical sessions encourages self-management and will help develop social networks.

Caregiver Approach and Support

• If more than one person is involved with feeding a child with MSUD, agree on a family approach, and all caregivers apply the same strategies in the same way.

• Use extended family members to help with food preparation e.g. making low protein bread, cakes, and biscuits. It is best if all family members receive education about MSUD.

• Once a month prepare low protein meals that can be frozen, so there are always 'ready meals' that are suitable to eat.

• Parents should try and support each other: swap recipe ideas, cooking tips and management tips on difficult practical issues. ■

*See article on page 13 regarding a new website with MSUD protocols.

References

•Schönberger S, Schweiger B, Schwahn B, Schwarz M, Wendel U. Dysmyelination in the brain of adolescents and young adults with maple syrup urine disease. Mol Genet Metab. 2004, 82: 69-75.

•le Roux C, Murphy E, Hallam P, Lilburn M, Orlowska D, Lee P. Neuropsychometric outcome predictors for adults with maple syrup urine disease. J Inherit Metab Dis. 2006, 29: 201-2.

•Packman W, Henderson SL, Mehta I, Ronen R, Danner D, Chesterman B, Packman S. Psychosocial issues in families affected by maple syrup urine disease. J Genet Couns. 2007, 16: 799-809.

•Ipsiroglu OS, Herle M, Spoula E, Möslinger D, Wimmer B, Burgard P, Bode H,Stöckler-Ipsiroglu S. Transcultural pediatrics: compliance and outcome of phenylketonuria patients from families with an immigration background. Wien Klin Wochenschr. 2005 117(15-16): 541-7.

•Packman W, Mehta I, Rafie S, Mehta J, Naldi M, Mooney KH. Young adults with MSUD and their transition to adulthood: psychosocial issues. J Genet Couns. 2012, 21: 692-703.

•Bartlett SJ, Krishnan JA, Riekert KA, Butz AM, Malveaux FJ, Rand CS. Maternal depressive symptoms and adherence to therapy in inner-city children with asthma. Pediatrics. 2004, 113: 229-37.

•Olsson GM, Montgomery SM, Alm J. Family conditions and dietary control in phenylketonuria. J Inherit Metab Dis. 2007, 30: 708-15.

•Hallam P, Lilburn M, Lee PJ. A new protein substitute for adolescents and adults with maple syrup urine disease (MSUD). J Inherit Metab Dis. 2005, 8: h665-72.

Jordan Bulcher's Experience with Dr. Lee's Buphenyl Study

Follow Up By Sandy Bulcher

From left to right is Alyssa Tran, Jordan Bulcher, and Mary Mullins (Alyssa and Mary are part of Dr Lee's research team). This photo was taken at Texas Children's Hospital in June when Jordan was participating in the Buphenyl study.

Jordan, my 23 year old son with MSUD, and I traveled to Houston, Texas again in June for the last phase of the Buphenyl trial (see last newsletter Vol 31, Number 1). For two weeks prior to going to Houston, he took the opposite medication (Buphenyl or placebo) of what he took earlier this year. Jordan didn't think that this drug tasted as bad as the one he took previously and he tolerated it better.

We spent two nights at the research center and again blood and urine tests were done. His intake of formula, food, and snacks was controlled by the staff and was very similar to what he consumed during the first phase. Jordan was comfortable during his stay and spent time doing his schoolwork, watching TV, and playing games.

If you or your child has been contemplating participating in the study, it is not too late. There is time available this fall or winter. Dr. Lee would like those with Mild or Classic MSUD with a variety of mutations to participate. If you would like to talk to me or Jordan, feel free to email me at dbulcher@aol.com or call at 740-972-5619. If you would like to talk to Mary Mullins, Dr. Lee's research nurse, she can be contacted by email at mullins@bcm.edu or phone at 832-822-4263.

Dr. Lee expects to be in the data collection phase for approximately 2 years. After that he will analyze his data and share his results.■

Body Mass Index in Adult Patients with Diet-treated Phenylketonuria

The protein-restricted diet is unique in many ways. One thing that always has acquaintances shaking their heads is the freedom with which those with MSUD can eat fats and sugars. When our children are little we struggle to get enough calories into them to prevent a breakdown of body tissue. In this wacky turned-around world, soda is good, beans are bad. French fries and potato chips are go-to items when away from home. My daughter used to eat the butter sitting on the table at restaurants, and still occasionally does when she needs extra calories. While my other kids drink water or artificially sweetened drinks, she will have a Coke or Pepsi.

Metabolic formulas are the backbone of the MSUD diet. As we clearly see from the stories we hear from around the world, access to metabolic formulas means the difference between life and death, life with normal physical and intellectual abilities and life with impairments. But what about all that fat and sugar they're loaded with to provide adequate calories? Might the MSUD diet result in other problems such as obesity and chronic disease while allowing our kids to live "normal" lives?

A new paper published in the Journal of Human Nutrition and Dietetics reports on research addressing this issue in individuals living with PKU in Great Britain (Robertson 2013). The researchers identified 236 individuals older than 16 years of age and obtained information on body mass index (BMI) and phenylalanine levels. 55% had a BMI indicating overweight or obesity. While high, this was consistent with the rest of the British population. The authors concluded that patients should be educated on a healthy low phenylalanine diet to prevent the development of chronic diseases.

This advice clearly applies to those following an MSUD diet as well. Most fruits and vegetables are naturally low in protein and high in antioxidants and other phytochemicals associated with good health. Vegetables prepared with olive oil will provide healthy fats for more calories. Swap sodas and other highly sweetened drinks (teas, lemonade, punch) with water, flavored water or seltzer, or sports drinks such as Gatorade which have about half the sugar and calories of other sweetened drinks. Let's make sure that the MSUD diet provides the nutrients known to enhance health while limiting those that may compromise it.

Robertson L.V., McStravick N., Ripley S., Weetch E., Donald S., Adam S., Micciche A., Boocock S. & MacDonald A. (2013) Body mass index in adult patients with diet-treated phenylketonuria. J Hum Nutr Diet. 26 (Suppl. 1), 1-6 doi:10.1111/jhn.12054

IDENTIFYING AND TREATING COGNITIVE FUNCTIONING DEFICITS

The National Center for Learning Disabilities (NCLD) defines executive functioning as "… a set of mental processes that helps connect past experience with present action". People use it to perform activities such as planning, organizing, strategizing, paying attention to and remembering details, and managing time and space. It affects our ability to:

- Make plans
- Keep track of time and finish work on time
- Keep track of more than one thing at once
- Meaningfully include past knowledge in discussions
- Evaluate ideas and reflect on our work
- Change our minds and make mid-course corrections while thinking, reading, and writing
- Ask for help or seek more information when we need it
- Engage in group dynamics
- Wait to speak until we're called on

http://www.ncld.org/types-learning-disabilities/executive-function-disorders/what-is-executive-function

NEW RESEARCH: COGNITIVE FUNCTIONING POST-TRANSPLANT

MSUD treatment has come a very long way. With earlier diagnosis, the availability of medical formulas and better treatment during metabolic crises, more people with MSUD are able to keep leucine levels under adequate control and live mostly independent and satisfying lives.

As discussed in this newsletter, researchers have turned their attention to the neuropsychological effects of MSUD. Just how does this disease affect the brain? How do we help schools identify the services our children need to ensure their success? Will transplant reverse deficits in executive functioning? (See definition above)

Paula McLaughlin and colleagues recently published a case study describing the results of neuropsychological testing in a 26 year old woman 2 years after she had a liver transplant. In addition to MSUD, she had been diagnosed with ADHD, anxiety, and depression in childhood. The authors noted that the seizures and hallucinations she was prone to pre-transplant had stopped, but she continued to struggle with planning, time management, and attention, all aspects of executive functioning. Abstract reasoning, impulse control and problem-solving remained areas of difficulty for her. While speech, coordination, reading and driving were improved, anxiety and depression were heightened and she was receiving ongoing treatment.

As we learn more about the brain and how it is affected by MSUD, researchers are hopeful that effective treatments will be incorporated into early childhood care. ■

New Website

Genetics and Health

In a time when searching for quality health information can be like searching for a needle in a haystack, Genetic Alliance is thrilled to announce the launch of its newest public resource:

Genesinlife.org

Genes in Life is a user-friendly resource for anyone interested in genetics and health which harmonizes many existing resources and tools in a one-stop source for general information related to health and genetics services.

On GenesInLife.org, individuals and families can learn how and why to collect a family health history and share it with a healthcare provider; understand the differences between various types of genetic testing and services, and figure out which genetics professionals to consult.

The site will also host interactive features including blog campaigns encouraging comments and discussion as well as an "ask the experts" page, allowing users to request more information about the topics they care most about.
Check us out at www.genesinlife.org

For more information on genesinlife.org, please contact Rachel Koren at rkoren@geneticalliance.org

Asian Cucumber Salad

5 cups sliced thinly cucumbers
2 teaspoons toasted sesame seeds
1 tablespoon low sodium soy sauce
Freshly ground black pepper to taste

Combine ingredients in a large bowl; toss and serve.

Makes 5 cups

Nutrition Info Per 1/2 cup
Calories: 12
Total Fat: 0g grams
Saturated Fat: 0 grams
Total Carbohydrate: 2 grams
Sugars: 1 gram
Protein: 1 gram (Leucine: 30 mg; Isoleucine: 20 mg; Valine: 20 mg)
Sodium: 54 milligrams
Cholesterol: 0 milligrams
Fiber: 0 grams

Submitted by Dana Angelo White

Pie Crust

1.25 cups wheatstarch
1/4 cup Crisco shortening
1/4 teaspoon baking powder
1/8 cup powdered sugar
1/4 teaspoon salt
Liquid coffee creamer
Water

Pre-heat oven to 350. Mix together wheatstarch, Crisco, baking powder, powdered sugar and salt until crumbly. Add liquid coffee creamer and water until the right consistency. Bake for 10-15 minutes
Yield: 1 pie crust

Note from Lois: I never did like pies until we revised one so that we could have a good pie crust too. We love pies now with this recipe. I wouldn't change for another one.

Submitted by Lois Stauffer

Basic Tomato Sauce

2 tablespoons extra virgin olive oil
1 clove garlic, chopped
1/2 medium onion chopped
1/2 teaspoon ground fennel
1, 28-ounce can crushed tomatoes
1 teaspoon granulated sugar
1 cup fresh basil leaves
Kosher salt and freshly ground black pepper

Forget about jarred marinara – this recipe is simple and better for you!
Makes: 1 quart

Heat oil in a medium saucepan. Add garlic and onion and sauté for 5 minutes. Add fennel and cook for 20 seconds, until fragrant. Add tomatoes and sugar; season with 1/2 teaspoon salt and black pepper to taste. Cook, uncovered, for 20 minutes, stirring occasionally. Add basil and season with additional salt and pepper, if needed. Puree sauce using an immersion blender* until smooth.

(*If you do not have an immersion blender, puree in a countertop blender in small batches. Make sure to hold the top of the blender closed with a dish towel while the machine is on.)

Nutrition Info Per 1/2 cup
Calories: 68 / Total Fat: 4 grams / Saturated Fat: 1 gram
Total Carbohydrate: 9 grams / Sugars: 1 gram
Protein: 2 grams (Leucine: 70 mg; Isoleucine: 40 mg; Valine: 50 mg)
Sodium: 202 milligrams / Cholesterol: 0 milligrams / Fiber: 2 grams

Submitted by Dana Angelo White

Chocolate Cake or Twinkies

1/2 cup granulated sugar
1/4 cup mayonnaise or miracle whip
3 tablespoons baking cocoa (omit for Twinkies)
1/2 cup water
1.25 cups wheatstarch
1/2 teaspoon baking soda
1.5 teaspoons baking powder
1/2 teaspoon vanilla
1/4 cup applesauce or grated zucchini
1/2 cup instant vanilla pudding

Preheat oven to 350°. In a Bosch mixing bowl combine sugar, mayonnaise, cocoa, water. Mix well, then add wheatstarch, baking soda, baking powder, vanilla applesauce and instant pudding For a white cake or twinkies omit the cocoa. Mix the cake batter for about 3 minutes. Bake 25-35 minutes for a cake, 15 minutes for cupcakes, and 11 minutes for twinkies (I use a brownie pan).

Submitted by Lois Stauffer

Cool Whip Frosting

1 package or 1/2 cup instant vanilla pudding
1 8 oz. carton Cool Whip

Pour liquid coffee creamer into a bowl and add other ingredients. Beat until it is the consistency of frosting.
Note from Lois: It is delicious and not sweet like sugar frosting. I use it for whoopies, twinkies and to decorate cakes.

Submitted by Lois Stauffer

Many thanks to Dana Angelo White and Lois Stauffer for submitting recipes! We no longer have a recipes editor as Glenda Groff has stepped down. Our readers appreciate sharing in any tasty recipes you have found or developed, so please send them in!

Cambrooke Foods

Cambrooke Foods is excited to announce two new low protein food products –**Toasted Pierogies and Marinara Minis**! Toasted Peirogies are low-protein pasta freshly filled with potato and cheese and covered in a crumb coating. They are perfect as an appetizer or as an entrée!

Toasted Pierogies go great with the other new product, Marinara Minis which are individually packaged cups of marinara sauce. Because Marinara Minis come in a single serving size, they are convenient and easy to take on the road. Marinara Minis are also suitable for low protein pasta products or as the sauce on Cambrooke's Tuscan Pizza Crusts.

Speaking of convenience, have you tried Camino PRO® Amino Acid Formula for MSUD? Available in ready to drink pouches, Cambrooke's MSUD formula line comes in fruit punch and piña colada. Each serving provides 15 grams of protein, a blend of vitamins and minerals and fiber.

To try a sample, or to place your order, call toll-free 866-5-456-9776, option 2 or visit our website at ***www.cambrookefoods.com.***

Cambrooke Foods can also be reached by fax at 978-443-1318 or by mail at 4 Copeland Drive, Ayer, MA 01432.

MSUD Management Survey

By Dianne Frazier

A survey to help direct the Genetic Metabolic Dietitians International (GMDI) to provide resources to accompany its Nutrition Management Guidelines (see: https://southeastgenetics.org/ngp) was included in the last issue of this newsletter. There were 43 respondents who represented a total of 51 individuals with MSUD. The responses were able to provide an overview of some of the management issues that you deal with everyday and insight about resources that may improve this management. A similar survey was available online for metabolic dietitians to learn how they are involved in MSUD management and what resources they feel are presently lacking.

While 7 adult respondents indicated that they had no contact with a metabolic dietitian, 47% of all respondents said that they had between 6 and >25 contacts per year. While 2 adults said they had no clinic visits, the remaining had between 1 and 6 clinic visits per year. The number of visits decreased as age increased. While 21% indicated that they had their leucine (LEU) levels checked only once or twice per year, the rest had more frequent monitoring: 4-50 times per year. Over one third of respondents said that they never checked urine for ketones, while an additional 25% checked "only as needed". Among the remaining respondents, there were several who used urine testing routinely: monthly – daily.

Respondents indicated that they used a wide variety of methods to plan their diets. Fifty percent counted LEU or LEU plus protein (PRO); 42% counted PRO or counted PRO and avoided high PRO foods and 8% simply avoided high PRO foods. Without knowing the LEU tolerance of individuals taking the survey, nor what their blood LEU levels are, it is difficult to assess whether more accurate food composition data would improve their clinical status. However, the overwhelming response to the questions about resources was that more extensive food composition data (LEU and PRO content) was needed.

MSUD Toolkit Workgroup

With the grant from the MSUD Family Support Group it was possible to assemble a "MSUD Toolkit Workgroup" consisting of: Amanda Andraos, Sandy Bulcher, Dianne Frazier, Caroline Homer, Julie McClure, Surekha Pendyal and Sandy vanCalcar. They analyzed the responses from the patients' and providers' surveys, collected and evaluated available resources, and set a priority list of resources to be developed. Along with this list, the workgroup also developed a system to guide the development and evaluation of new and existing resources. The first four resources that will be developed, enhanced or revised are: low LEU/PRO food lists; pictorial information for low literacy or ESL (English as a second language) families; educational material for children; and a booklet for pregnancy among women with MSUD. ■

THE BULCHERS VISIT AN MSUD FAMILY IN COSTA RICA

By Sandy Bulcher

My husband, Dave, and I decided to take a vacation to Costa Rica. Like Wayne and Joyce Brubacher, we like to meet MSUD families from other states or countries when we travel. I was aware that the Abarca Mora family lived in San Jose, Costa Rica and contacted them about getting together during our trip. We had some difficulty communicating due to a language barrier, but with the help of a Spanish speaking friend we were eventually able to arrange a time and place to meet.

On the evening of our first day in San Jose, Randall Abarca Mora, his wife Johanna, and their 6 year old MSUD daughter Stacy, met us at our hotel. Dave and I were very excited to meet and spend time with them. Randall's friend was present to assist with translation. We spent most of our time talking about our children and their lives with MSUD. Randall and Johanna shared their struggles in obtaining medical formula and low protein food for Stacy. They are considering forming a Costa Rican MSUD support group. Hopefully, as a group they will have more influence and be able to make changes that improve the lives of the MSUD children and adults in Costa Rica.

We have always found it very rewarding to meet new MSUD families when we travel. If your travel plans allow it, we would encourage you to consider it as well. ■

From left to right: Sandy Bulcher, Dave Bulcher, Randall Abarca Mora, Johanna Abarca Mora, and in front Stacy Abarca Mora, age 6 MSUD

Introducing NBS-MSUD Connect!
NBSCONNECT.ORG

The Newborn Screening Connect patient registry (NBS Connect) is a web-based self-report patient registry curated by professionals. This resource is for those affected by certain disorders included in the newborn screening panel. The registry has been developed by national experts in the field of NBS disorders at the Department of Human Genetics at Emory University, and serves as a support network for parents, guardians and individuals with inborn errors of metabolism.

Extensive development of the registry is occurring via a phased approach which began with the launch of NBS-PKU Connect for Phenylketonuria (PKU). We have now concluded beta testing and we are launching the next phase with NBS-MSUD Connect for Maple Syrup Urine Disease (MSUD). We will continue expanding the registry to include other disorders in the NBS panel recommended by the American College of Medical Genetics (ACMG).

NBS Connect brings together patients, families, parent organizations, professionals, and industry in one forum. Professionals and industry are able to share clinical trial information with patients, professionals have access to de-identified patient survey data, patients and families are able to connect with one another and access useful tools such as recipes and educational resources.

We ask all adult patients and parents or guardians of individuals with PKU or MSUD, to visit the website at nbsconnect.org, to register and complete their participant profiles. Participants will have access to disorder specific education materials, information on the latest research and clinical trials, recipes, interactive health tracking systems, "Ask an Expert" tools and more. Patients who take advantage of the resources provided, become empowered to make more informed healthcare decisions.

This registry is an asset both for forming connections between consumers and for building a qualitative database for future research. Interest in this project continues to grow and is currently gaining an international presence.

If you have any questions about the patient registry or require brochures for distribution, please contact Yetsa Osara, MPH at coordinator@nbsconnect.org or 404-778-0553. **Register at www.nbsconnect.org today!**

A HRSA SUPPORTED PARTNERSHIP — GRANT #H46MC24090

Anna Elizabeth Moyer found a way to help and support children with MSUD and their families. At her death, she gifted her estate to the MSUD Family Support Group to "support research and to disseminate information concerning the disease."

Anna was born in 1917 and lived most of her life before knowledge of MSUD was common. Anna learned about MSUD from Joyce Brubacher, as Joyce's mother and Anna were friends. When Joyce and Wayne Brubacher's oldest son, Monte, died in 1974 as a result of complications resulting from MSUD, Anna was deeply touched.

Anna directed that the entirety of her estate go to help those with MSUD and to further MSUD research. Anna passed away in October 2011 at 94 years of age. The MSUD Family Support Group is grateful to Anna Elizabeth Moyer for her generous donation.

Marlon Falconer, Classic MSUD and 7 years post transplant welcomed his new sister, **Mar**, this winter. She was born MSUD free. He is a great big brother, loving, caring, and doing great health wise.

Jenna Kiel graduated this spring from Michigan State University, School of Social Work. She'll be attending Western Michigan University in the fall for her MSW (Master's In Social Work).

Thiamin-Responsive
Maple Syrup Urine Disease

By Brenda Abdulahad
Nutrition Student

Thiamin is a vitamin (B1) found in a variety of foods including meat, legumes, and whole, fortified and enriched grain products. Thiamin's main role in the body is to act as a helper to enzymes used to release energy from foods. Thiamin also plays a role in fatty acid synthesis, membrane and nerve conduction and amino acid metabolism.

The metabolism of branched-chain amino acids (BCAA) involves several enzymatic steps and complexes. The first step involves removing the amino group to create alpha-ketoacids. This step is catalyzed by an enzyme known as branched chain aminotransferase (BCAT), and occurs normally in MSUD. The next step involves a branched-chain alpha-ketoacid dehydrogenase complex (BCKAD). MSUD is caused by a defect in this enzyme complex, resulting in a buildup of BCAAs and their alpha-ketoacids. Thiamin is part of a cofactor needed for this enzyme to work.

One form of MSUD is considered to be thiamin-responsive. This variant of the disease is less severe than the classic form, and has some enzyme activity. The daily requirement for thiamin in healthy people is approximately 1.1 mg daily for adults, but the amount needed to improve enzyme function is much greater and depends on the amount of enzyme activity present. Thiamin dosages used to treat MSUD range from 10-100mg each day. Individuals who have thiamin-responsive MSUD can also tolerate more protein in their diet as compared with other more severe types of the disease.

The first observed thiamin-responsive patient was reported by Scriver and associates in 1971. This French Canadian female infant was admitted to Montreal Children's Hospital with moderately elevated plasma BCAA concentrations. She was provided with a 10 mg per day oral supplement of thiamin hydrochloride and her plasma BCAA concentrations were drastically reduced to normal levels without restricting BCAA intake. The withdrawal of the vitamin supplement caused a fast return of plasma BCAA concentrations to the pre-thiamin levels. This was followed by another sharp decline of BCAA concentrations upon reintroduction of the thiamin supplement (Chuang, 2006).

Researchers hypothesize that large doses of thiamin increase the amount of the cofactor which is needed for proper enzyme function, allowing the enzyme to function normally (Rosenberg 2008 pg 669). Large doses are safe as they do not cause toxicity and excess amounts are excreted in the urine.

This method of treatment only works for MSUD individuals who are thiamin-responsive. Those with classic MSUD do not respond as they have minimal or no enzyme activity of the BCKAD complex. Thiamine supplementation is not an alternative to diet for individuals with this type of MSUD. It should be understood that while thiamine is a vitamin, when administered in these very large doses it acts more as a drug making monitoring by a physician essential. ■

References:

Chuang, D., Chuang, J., & Wynn, R. (2006). Lessons from genetic disorders of branched chain amino acid metabolism. The Journal of Nutrition, 136(1), 2435-2495.

Rosenberg, R., DiMauro, S., Paulson, H., Ptacek, L., & Nestler, E. (2008). The Molecular and Genetic Basis of Neurologic and Psychiatric disease. (4th ed., p. 669). Philadelphia: Lippincott Williams & Wilkins.

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MAPLE SYRUP URINE DISEASE FAMILY SUPPORT GROUP

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