



MSUD NEWSLETTER

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ON-LINE FOOD LIST LEUCINE AND PROTEIN CONTENT OF FOOD

Dianne Frazier, PhD, MPH, RD
Professor Emeritus
UNC School of Medicine

The Genetic Metabolic Dietitians International (GMDI) completed the Guidelines for the Nutritional Management of MSUD in 2013. With the help of a grant from the MSUD Family Support Group, the GMDI workgroup surveyed both the MSUD community and metabolic dietitians to determine the unmet needs for educational resources.

Using this needs assessment, the MSUD Toolkit was



designed to provide a practical guide to assist clinicians implementing the Guidelines. Linked to the toolkit are resources developed or adapted for use with this population. One of these is a food list containing the leucine and protein content of foods appropriate for individuals limiting their leucine intake. This was a resource requested by nearly 100% of the survey respondents. It is now available online to be downloaded, printed, or searched at <http://gmdi.org/Resources/Leucine-and-Protein-Content-of-Foods>. The instructions for these functions are on the website.

The nutritional information was obtained from the GMDI nutrient analysis software MetabolicPro. Once the entire toolkit is published, clinicians will be able to access, and modify if necessary, other resources they deem appropriate for specific individuals with MSUD. S

SAVE THE DATE

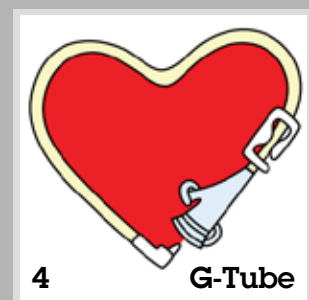
MSUD SYMPOSIUM 2016

MSUD SYMPOSIUM 2016 will be held in Raleigh, North Carolina at the Embassy Suites Raleigh-Durham Airport/Brier Creek on Thursday June 23rd to Saturday June 25th.

Look forward to seeing you!

Financial Assistance Available. See page 6

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EDITOR'S NOTE - Fall 2015

By Karen Dolins

Communication sure has changed over the past couple of decades. Does anyone still write letters? My handwriting has gotten so bad that I struggle over short thank-you notes!

When I first joined this support group after the birth of my daughter Hannah (Classic, 21 years), I was thrilled to get this newsletter in the mail. I certainly didn't know anyone else with this rare disease, and I enjoyed the connection I felt with others for whom MSUD was a part of their reality. Now I enjoy reading posts on the Facebook page, although I must admit I'm not a regular user. I also get MSUD news through email, either from advocacy organizations or subscriptions to scientific articles. And of course we have our website managed by Eddy Wang at www.msud-support.org.

When our board met in June (see President's note by Ivan Martin), effective communication was high on our agenda. We discussed the fact that many organizations are reducing the number of print newsletters they produce, with some opting to do away with them altogether. We now have more efficient ways of delivering the news. Rather than delaying communication for months while we gather information, go through the editing process, publish,

address, and mail the print newsletter, we can post items of interest on our website, on our Facebook page, or send an eblast. This does 2 things for us: it gets important information to you faster, and it saves our organization money which we can then use for other purposes.

We have decided to take a middle of the road approach. We will continue to print 1 newsletter annually, and communicate throughout the year through our website, FB page, and occasional eblasts. This means you will hear from us more often! It also means that you have an easy way to let us know what you're thinking, feeling, and how we can help. We do hope that our international members will agree to receive our newsletter electronically. Please let us know.

This issue includes family stories – thank you to the Bricker family and the Vaidya family for sharing. We also provide updates on research that has recently been published in the professional journals, recipes from Dana White, and of course information on our upcoming 2016 Symposium.

Please feel free to get in touch as often as you'd like. You can reach me at Karen.dolins@yahoo.com. \$



Introducing NEW infant formula for MSUD!

Nutricia is committed to providing families with the latest in innovations to metabolic formulas. We are proud to introduce the new **MSUD Anamix® Early Years** for infants diagnosed with MSUD. It is the only metabolic infant formula to contain DHA & ARA and prebiotic fiber, making it closer to breast milk than our previous infant formula. The MSUD Anamix Early Years is the latest addition to our line of MSUD formulas, including Complex® Junior, Complex® Essential and MSUD Lophlex® LQ. For any questions about this or any other MSUD formulas, please contact your metabolic dietitian, or feel free to call us at **1-800-605-0410**.



READING LIST

By Sandy Bulcher, mom of Jordan, age 25, Classic MSUD

Did you know there was a fiction book written with references to MSUD?

A few years after our son Jordan was diagnosed with MSUD, a friend told me that she had read a crime fiction novel whose killer had MSUD. I don't typically read murder mysteries but my curiosity got the best of me, so I purchased the book *Post Mortem* written by Patricia Cornwell and published in 1990. In the book, a medical examiner is trying to solve the murders of several women who have one thing in common: the smell of maple syrup left behind by their killer. The story implies that the killer has a rare metabolic disorder. The medical examiner uses the latest advancements in forensic science including DNA to help solve the crime.

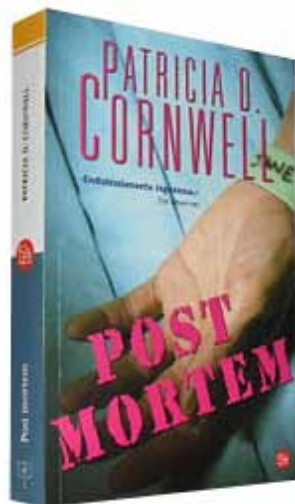
Even though it is an intense story, I found the references to MSUD rather amusing and wanted to share it with all of you as you may enjoy reading it also.

Synopsis

Postmortem is a crime fiction novel by author Patricia Cornwell. The first book of the Dr. Kay Scarpetta series, it received the 1991 Edgar Award for Best First Novel.

The book is loosely based on the killings of Timothy Wilson Spencer, who was active in Richmond, Virginia, at the time Cornwell was working at the morgue as a computer analyst.

Under cover of night in Richmond, Virginia, a human monster strikes, leaving a gruesome trail of stranglings that has paralyzed the city. Medical examiner Kay Scarpetta suspects the worst: a deliberate campaign by a brilliant serial killer whose signature offers precious few clues. With an unerring eye, she calls on the latest advances in forensic research to unmask the madman. But this investigation will test Kay like no other, because it's being sabotaged from within and someone wants her dead. §



Abbott Nutrition Metabolic Conference



Sandy Bulcher VP, MSUD Family Support Group

One of the goals of the MSUD Family Support Group is to increase our presence at meetings of metabolic clinicians. In April of this year, I had the opportunity to be an exhibitor at the Abbott Nutrition Metabolic Conference in San Diego, CA. The conference was held at the beautiful Loews Coronado Bay Resort and there were over 100 professionals, primarily metabolic dieticians, in attendance.

I provided literature about the support group to the attendees and encouraged them to inform their MSUD families about our organization, especially new families. A few professionals did not know that our organization existed and some did not know about our research projects or biennial symposiums. During the conference, I reconnected with the National PKU Alliance representative, Christine Brown, and was updated on the activities and projects of the PKU community.

The speakers and topics were interesting, however networking with the professionals was invaluable. Through networking, I learned many new things, including that MSUD is higher in the African American population and in those from El Salvador than I had realized. Hopefully our organization will be able to better connect with these families in the future.

The MSUD Board is committed to advocating for MSUD at professional meetings and plans to send a representative to one or more meetings each year. §

Making the Decision about a Gastrostomy Tube (G-Tube)



By Heather Bausell, RD, LDN - Metabolic Nutritionist, Ann & Robert H. Lurie Children's Hospital of Chicago

Introduction:

The treatment of maple syrup urine disease (MSUD) requires daily, consistent medical food (formula) consumption. Compliance with formula intake can be a challenging aspect of the treatment. Children and adults with MSUD may be vulnerable to behavioral, emotional, and medical problems that can interfere with daily activities including formula consumption.¹ When illness occurs, lack of appetite can make it difficult to consume medical food. The pressure to take the formula multiple times a day can be exhausting, overwhelming and discouraging for the family and the person with MSUD.

As a result of these obstacles, some families decide to move forward with the placement of a gastrostomy tube (G-tube) to alleviate some of the stress that is associated with daily formula consumption and formula intake during illness. Making the decision to have a G-tube placed can be difficult for families. The goal of this article is to discuss points to consider when making the decision to have a G-tube placed and to share feedback from two families that have experience with MSUD treatment and the use of a G-tube.

The Perceived Barriers and Challenges:

When the medical team becomes aware of the struggle around consuming medical food, they often recommend G-tube placement to the family of a child with MSUD or to an adult with MSUD. The decision making process can often be characterized as a time of uncertainty, stress and conflict. Some people perceive the need or the consideration of a G-tube as a loss of normality, a sign of disability, or a sign of failure.² These are perceptions that often keep families or people with MSUD from making the decision to move forward with G-tube placement.



There are several common barriers or misconceptions that prevent families from feeling comfortable with the placement of a G-tube. One example is the belief that a G-tube will limit the ability to be physically active. Tube feeding itself should not limit a person's ability to be active. Even swimming is possible with a G-tube! Another misconception is that once the G-tube has been placed the individual with MSUD will never drink formula again. Some children and adults with MSUD choose to drink their formula on a regular basis and only use the G-tube during illness. Others use their G-tube for daily formula intake and know that there is also the option to drink it by mouth. A final misconception is that a G-tube is forever. When an individual has shown the ability to consume their medical food consistently and without difficulty, they may consider the removal of the G-tube. This decision is usually made in collaboration with the medical team. The removal of the G-tube does not require surgical intervention in most cases, because the G-tube site will usually close on its own once the G-tube is removed.³

Quality of Life:

G-tube placement is one way to be proactive in the adherence of dietary treatment of MSUD. Infants, children and adults with various medical conditions, including MSUD, have G-tubes and use them as a tool to help them be successful in their medical treatment. A quality of life study was conducted in children and parents affected by inborn errors of metabolism (IEM) who had a restricted diet. Of those who participated, 24% of the families in the study were MSUD families. The study used questionnaires to assess both the child and the parent's quality of life in several different categories. The study data

showed that the score for psychological well-being was higher in children that had used a type of enteral nutrition (tube feeding) at some point. The parents of children that had G-tubes also reported higher scores for physical health and social relationships. It has been reported that a G-tube can decrease parent's stress around the care of their child.⁴

Shared Experience:

Below is an excerpt of conversations with two MSUD families discussing their experience with deciding whether or not to place a G-tube and the process they went through in making that decision.

What was the hardest part about deciding to get the G-tube placed for your son?

Family 1: Our team would ask about placing a G-tube from the time Mason was two years of age. I would always say NO! One of my biggest issues in the beginning was I thought it would be extremely noticeable. It's small, you barely notice it.

How has getting the G-tube changed your MSUD management?

Family 1: It was a struggle to get Mason to drink his milk. We would bribe him and spend many hours getting Mason to drink his milk. Mason, who at the time was six years old, is the one who really made the decision that it would be a great idea, so we had the G-tube placed. This has made the management of MSUD a whole lot easier. It makes a big difference when he is a little sick or levels start to go up, we can manage at home a lot more than having to be put in the hospital. There are no more battles with Mason to drink his milk. We just put it into his G-tube and we are done. This process takes all of three minutes if that. We are able to focus on fun things to do and not worry if he is getting enough or all of his milk. Mason is now thirteen years old, he is able to do his own milk. He has been doing this since he has been in second grade.

Is your family's quality of life different since the G-tube placement?

Family 2: Our son was diagnosed at birth through new born screening; we put in the G-tube just after he turned three. It's really taken the pressure off our son. The quality of life is much better. Talking about MSUD with an almost six year old is tricky; the G-tube sort of adds another layer to understand, but

the day to day is easier. We use the tube as back up and we were able to loosen our schedule because of that. I remember the first time we really felt like we benefited from the tube was that 4th of July. We stayed out late to watch fireworks. We were a little off our strict routine. When we got home he went to sleep and we fed him through the tube. He really loved the fireworks, and had a blast. We saw him feeling kind of free in the moment for the first time.

What would you tell a family or person with MSUD who is contemplating getting a G-tube?

Family 2: I would have made the decision quicker. It still would be hard, but sometimes with a life threatening medical condition your brain has to call the shots and the heart has to catch up later. My heart is still catching up sometimes, mostly when I have to entertain my son's questions, but he doesn't remember his life without the G-tube.

Support and Resources:

The decision to place a G-tube can be difficult for parents to make. Therefore it is imperative to develop a positive and supportive relationship with the metabolic team. Collaboration and good communication with the medical care team is critical. It is important to have ample time to ask appropriate questions about the use, the purpose, and the placement procedure of a G-tube. Answers to these questions may greatly relieve any fears or concerns. Emotional support from friends and family through the decision making process is also important.⁵ Several G-tube focused support groups are available. The Feeding Tube Awareness Foundation <http://www.feedingtubeawareness.com> has a great parent guide to help navigate some of the commonly asked questions about G-tube use. Speaking with another family that has G-tube experience can also be helpful for support in making the decision.

Conclusion:

The treatment of MSUD requires daily medical food consumption which can create challenges with formula intake compliance. Infants, children, and adults with MSUD use G-tubes as a tool to be successful in their medical treatment. A G-tube is one way to be proactive in the adherence of dietary treatment of MSUD. Ample support from family and the medical team through the decision making process about G-tube placement is essential. §



(G-tube cont. on page 6)

(G-tube cont. from page 5)

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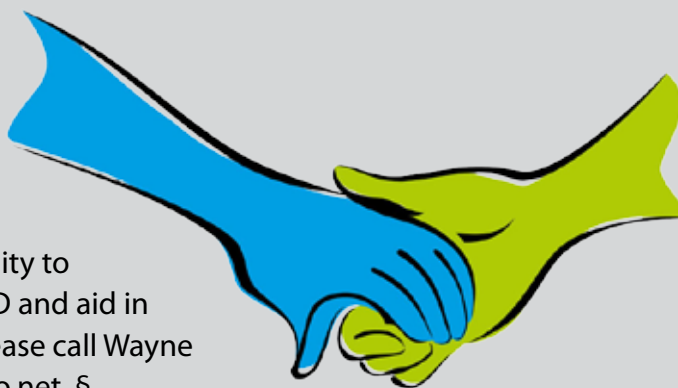
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Financial Assistance Available to Attend the 2016 MSUD Symposium

The United Services Foundation is again graciously supplying funds for the MSUD Family Support Group to help families and individuals attend the 2016 Symposium. This 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, but others may also apply. Funds are limited, so let us 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 2016. Late applications do not allow enough time to obtain visas and make airline reservations. We want to make it possible for all interested persons to attend. For information contact Wayne and Joyce Brubacher at 574-862-2992 or e-mail: wjbrubacher@afo.net.

Opportunity to get involved and meet people from around the world!

If you have a computer, and would be interested and willing to help with the financial assistance program, please contact the Brubacher's. Help would be much appreciated, and this is an opportunity to have contact with other persons involved with MSUD and aid in helping them attend the Symposium. For details please call Wayne or Joyce at 574-862-2992 or e-mail: wjbrubacher@afo.net. §



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Tia's Tale

22 months old

By Vaishnavi Vaidya (Tia's mother), Columbus, Ohio

22 months back... During Thanksgiving time in 2013 we were excited, at the same time nervously waiting for our daughter to be born. Everything went very smoothly and we named her "TIA" (TIA meaning Goddess: Goldy in Greek). She was perfectly fine and a healthy baby at the hospital. After coming home, she cried throughout all days and nights. Initially we thought she was being fussy due to gas but that crying was not normal. She reduced drinking breastmilk and eventually completely stopped. After few days at home she hardly opened her eyes, only kept crying and sleeping due to tremendous cry. The screening results came back little late due to the Thanksgiving week. On the 6th day of her life I received a call from a nurse saying one of her screening test was not normal and asked that we have her amino acid tests redone. She also scheduled a follow up appointment for the next morning with a pediatrician for ketone detection in urine. (We were not told what was wrong with my child. I asked that to the nurse, she said to get her amino acid test done and if results come back abnormal again then the doctor will let us know.)

On next day around 8 o'clock, we headed to the pediatrician's office and waited so long for her to urinate for the ketone test as she was dehydrated. Finally we got a little bit of her urine in the cotton balls and the test was performed around 11 o'clock. The test was positive for ketones, and the pediatrician directed us to go to Nationwide Children's Hospital Emergency room. He said Genetics and Metabolic doctors would be waiting for Tia and they



Tia, Classic MSUD, Age 22 months

would give us further information. At the hospital we met Dr. Dennis Bartholomew and his team who on the way to Emergency room explained about MSUD, a rare metabolic disease. They started her IV immediately after admission to get her hydrated as she had lost one pound in a week from not drinking. On the second day of admission, her formula was going through a naso-gastric tube but Tia started having reflux so they inserted a naso-jejunal (NJ) tube. As her leucine levels didn't drop significantly from her initial level of 3000, the doctors decided to move her to ICU for most immediate care. Finally after few days her levels stabilized and she opened her eyes. As the levels started to come down she started drinking a little from a bottle but continued to get formula through the NJ tube. We came back home after 22nd day of birth where we continued to feed her via mouth and NJ tube. Within a few days, her NJ tube was removed as she started showing interest in drinking her formula.

(Tia cont. from page 8)

During the first year of Tia's life, her leucine levels fluctuated a lot and she had to go to the emergency room a couple of times. She reduced drinking her formula both times, and I was told that if she doesn't have at least 60-70% of her allocated formula for 2 days, then she should be seen by a physician in the ER. We were sent back home without being admitted both times as all of her tests were normal and we switched her to a sick day diet to get her on track. (Now also she reduces her formula intake sometimes even though her ketone tests are negative.)

Family and friends back in India wanted to meet our newborn. Knowing her condition had been stable for some time, we made a decision to go for a 20 days trip to India when she was 14 months old. I didn't want to change a single thing about her diet during the trip so we shipped out everything before we went there including formula, low protein baby food, juices and nursery water supply worth a month. In India, the metabolic clinic was around 700 miles from my parent's house. During our 2nd week, she developed diarrhea and vomiting which lasted for half of the week. We kept giving her formula, juices and water during that time to keep her hydrated.

We did attend a marriage of my cousin back in India. Tia spent a good time, seeing so many people around playing with her. She became more social and started to get along with most of the family and friends. Everyone was really happy to meet her and mostly, we were very happy to see her enjoying herself. Overall it was a good memorable trip back home. We have seen a major change in her nature of

interaction. Before the India Trip she was very introverted and wouldn't go to anybody except us and after the India trip she was completely a different Tia to us, more social and happy. After the India trip we took other trips to California (Disneyland California, Los Angeles, San Diego and San Francisco) and Niagara's falls, NY. We brought formula, medicines, foods, etc. wherever we went with her. The local metabolic doctors were informed that Tia would be coming there and we also had their



Vaidya Family

contact information just in case we needed them. Tia had two hospitalization during her second year. One was due to an ear infection and resulted in reduced formula intake (but at that time her leucine levels were low) and another hospitalization was due to increased leucine levels.

We are eagerly waiting for outcome of Buphenyl trial by Dr. Lee. Looking at past months no doubt we had some ups and down but seeing her running around and calling us Mummy and Daddy we forget everything. §



Johnny Bricker: Our MSUD CF (Cystic Fibrosis) Warrior

By Ashley Bricker, Mom

I'd like to introduce you to Johnny, our little MSUD and Cystic Fibrosis Warrior. Johnny was born on April 11, 2015. We had no idea throughout my pregnancy that he had any genetic diseases or disorders as I opted out of genetic testing. No matter what the results of a test would have been, I was still having my little boy!

Johnny was diagnosed with MSUD from his newborn screening when he was 4 days old. We were told to

go to Children's Hospital of Philadelphia immediately, which is about 2.5 hours away from where we live in Dauphin, Pennsylvania. The following day, when we were at CHOP, he was also diagnosed with Cystic Fibrosis (CF), another genetic disease. The defective gene in CF does not allow sodium to be released into the body. This makes mucus very thick, causes persistent lung infections and progressively limits the ability to breathe. If Johnny gets a simple cold it can take him weeks to get rid of it because he cannot properly clear the mucus that houses the infection. CF also makes it hard for Johnny to gain weight because the mucus lines his intestines and stomach making it difficult to absorb nutrients. He is only the second child in the world to have both these diseases simultaneously. Neither my husband nor I had any idea we were carriers of both these diseases and who would have thought our little man would end up with both of them?!

After a week at CHOP getting Johnny's leucine levels down, we were finally allowed to go home! However, we ended up back at CHOP within 4 days of being discharged. While we were in the hospital the first time, Johnny contracted Rhinovirus. He was air lifted immediately back to CHOP where he was placed on a C-Pap machine to help him breathe. His leucine was elevated, but only slightly, thankfully! Johnny and I lived in the NICU for 2 weeks. Once he was able to come off the C-Pap he was moved to the Pulmonary floor for a week. After 3 long weeks at CHOP we were able to go home again. Johnny was healthy! Thankfully, we have been home ever since. Our little guy has spent more time in the hospital than both my husband and I combined over our entire lives.

We are currently considering what options we have for the management of Johnny's MSUD for the rest of his life; dietary management or a liver transplant. CHOP has not spoken to us about this yet, but we know it's a discussion we would like to have as Johnny gets older. He's only 4 months old so we know we have time. Our decision will have to take into account his CF, which throws a whole other ball into the court. Johnny's daily CF care involves giving him special enzymes before every bottle or every time he eats (when he can have real food). We also have to do nebulizer treatments with chest physical therapy twice a day. The treatments increase to four times a day when he gets sick or has a

(Johnny cont. from page 10)

cough. Each treatment takes an hour. We have amazing teams of doctors, though, so I know we will make the right decision and the best decision for our family and especially for Johnny.

Johnny has a big sister at home who is 3 ½. Faye is a perfectly healthy child who loves and accepts her little brother wholeheartedly. She loves to help make sure he has all his supplements and reminds me of everything I need to do when it comes to managing his CF.

Johnny's Dad and I are extremely grateful for newborn screening. We are so blessed that Johnny never presented in a metabolic crisis, though his leucine numbers were high. We are also fortunate that he has not been negatively affected developmentally and that we have been able to keep his numbers in check while we are at home.

I am so very thankful we found this MSUD support group. I know I will have many, many questions about diet and transplants in the future. In the meantime, I'd like you all to meet Johnny, our amazing little warrior who is going to defy all the odds in his life! §



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IN THE MEDICAL JOURNALS



MSUD IN GALICIA, THE NORTH-WEST REGION OF SPAIN



Dra María L. Couce, Dra María José de Castro

Metabolic Unit from Hospital Clínico Universitario de Santiago de Compostela. Santiago de Compostela. Spain.

MSUD Newborn screening in Galicia and Spain

Galicia is a region in the North-West of Spain where extended newborn screening (NBS) with the use of tandem mass spectrometry technology has been well established since 2000. In fact, we have been its pioneers in Spain and one of the first European countries to implement it. Diseases screened by NBS include maple syrup urine disease MSUD which is detected by measuring the whole blood combined leucine-isoleucine concentration and its ratio to other amino acids such as alanine and phenylalanine. MSUD has been recently included in the newborn screening from other Spanish regions, however it is not officially recommended for all the territory.

Our Inherited Metabolic Disease Center in Galicia has been designated as one of the seven National Reference Centers in Spain, and we receive patients from all over the country, Portugal and South America.

Once a neonate is identified, how quickly are they treated?

We have developed a protocol for the steps to

follow when a patient is detected by NBS. First the neonate is identified. If the results are very abnormal being suggestive of a severe pathology, our staff from the Metabolic Unit contacts the family by phone and informs them about the significance of the results and what they need to do. Our staff knows perfectly the evolution, prognosis and available treatments for these diseases.

Usually, it is necessary to act very fast when a neonate with MSUD is detected, so we advise the families to come to our Center to manage the patient. Both the Laboratory and the Clinical Unit have an efficient Emergency Attention Service in order to immediately assist these patients.

Prevalence and evolution of patients with MSUD detected by NBS

An estimated prevalence of 1 in 185,000 newborns with MSUD has been found in the world [1]. However, in certain communities there is an over-expression of this entity, such as the Mennonite [1,2] and in our region, Galicia, where the reported incidence is 1 in 52,541 newborns [3]. At this moment we have 7 patients with MSUD detected by NBS and all of them, except 2 with intermediate forms, are classical MSUD.

Those newborns with classical MSUD already exhibited symptoms of intoxication with elevated levels of leucine ($> 1500\mu\text{M}$) at the moment of detection (usually first seven days of life), although encephalopathy with signs of cerebral edema and coma was only detected in 2 out of 8 patients. One of these 2 patients was detected in 2001 when screening was advised at 5-8 days of life, showing the importance of early NBS. We now screen at Day 3.

None of our patients have required hepatic transplant, and they are all managed with dietary and pharmacologic treatment. During follow-up patients received not only a dietary leucine restriction, according to age and tolerance, but also valine, isoleucine and thiamine (100- 300 mg per day)

supplementation. In addition, it is well-established that oxidative stress contributes to brain damage in MSUD, and the use of appropriate antioxidants offers new perspectives for the prevention of the neurological damage in MSUD [4]. Our patients, according to the control and treatment protocol also receive vitamin complex with vitamin A, vitamin E and a frequent intake of selenium. The micronutrient profile is analysed annually providing specific mineral and/or vitamin supplements if deficiencies are detected. We have detected selenium deficiency in several patients.

Metabolic formula is free for the affected families in Spain, and in Galicia its distribution is centralized in the nearest hospital to their residence.

The main goal is to maintain leucine concentrations below 300µmol/L and, in children under 6 years old, to keep this level below 200µmol/L, with isoleucine and valine levels between 200-400µmol/L, controlling the normal range concentrations of glutamine, alanine, tryptophan, tyrosine, methionine and the ratios Leu/Tyr and Leu/Ala.

During an acute intercurrent illness the treatment protocol is carefully managed with a cessation or reduction of the protein intake to 50% for 24h-48h, depending on the severity of the illness, whilst providing a high energy intake with an extra 20% of caloric requirements through carbohydrates, lipids and double dose of carnitine, valine and isoleucine. In case of vomiting or clinical deterioration, an urgent hospital admission for intravenous glucose infusion without branched-chain amino acids (BCAAs) is recommended. The clinical course is subsequently monitored. Currently in Spain, a parenteral amino acid mixture without leucine, valine and isoleucine is available and we find that it brings our patients greater safety.

Cognitive function is assessed in all of our patients by the Psychomotor Development Index (PDI) or the Intellectual Quotient (IQ) giving normal results. One patient with an enzyme activity of 4% (moderate phenotype) and without neonatal encephalopathy developed a mood disorder (based on DSM-IV criteria) which responded favorably to standard antidepressants. We hypothesize that this may be related to higher mean leucine and BCAAs levels in this child as

measurements were performed much less frequently than recommended.

We believe that it is very important for achieving optimal metabolic control that the measurement of BCAAs in a dried blood spot sampling (leucine, isoleucine and valine) is performed. This is sent directly by the parents to our laboratory. We recommend that families monitor BCAAs levels once per week, which is usually not practical without a "send-in" filter paper method.

We have recently conducted a study assessing our data from MSUD patients in collaboration with other three Spanish regions [5] with the objective of comparing the evolution between patients detected early by NBS or late. Our study results support that NBS improves prognosis of MSUD patients. Even for those not detected by NBS, an aggressive treatment together with a close monitoring of leucine levels improves neurological evolution.

Conclusions

1. The inclusion of MSUD in the NBS programs with early sample taking improves the prognosis of these patients.
2. In order to achieve an optimal metabolic control of MSUD leucine levels should be kept as closest as possible to the normal range (between 100 to 300 µmol/L).
3. When decompensation is highly suspicious, BCAA measured in a dried blood spot allows us to obtain the sample at the patient's home and to know in a few hours the results in order to hasten the therapeutic management.
4. The availability of a parenteral amino acid mixture without leucine, valine and isoleucine brings patients with MSUD a greater safety in their management.

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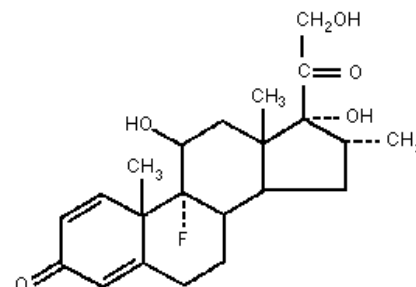
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By Karen Dolin

Cerebral edema (swelling of the brain) commonly occurs when a person with MSUD is in metabolic crisis. As cerebral edema has the potential to cause brain damage, prevention and effective treatment of cerebral edema is a major focus of clinicians. The precise mechanism by which high levels of leucine damage the brain are not known. This study used rats to look at the effect of branched-chain amino acids (BCAAs) on the brain, and examined the effect of dexamethasone, a steroid drug which has been found effective in treating cerebral edema resulting from brain tumors and other causes.

The authors demonstrated that elevated BCAA levels increase the permeability of the brain, allowing greater amounts of fluid and small molecules to enter. They also found that when rats were given dexamethasone, permeability of the brain, brain swelling and brain damage was reduced. §

Figure 1. Dexamethasone



Visit our website at

www.msud-support.org

to find recent and past newsletters and more.



Also, join the growing group over at Facebook:

www.facebook.com/groups/2220742408



From the President's Desk

By Ivan Martin

Last December Wayne Brubacher informed the MSUD Board of Directors that he was stepping down as president. With some reservation, we accepted his resignation. Please join us in thanking Wayne and Joyce for their many years of service. Although they want to be relieved from the responsibility, we will not be allowing them to disappear from the scene! We plan on keeping them involved, especially during the symposiums.

On June 27, the MSUD Board of Directors met at the Embassy Suites Hotel in Pittsburgh, Pa. The location was chosen for two reasons: it was a central location for travel and also allowed us to check out the hotel and the area restaurants as a possible future symposium location.

At this meeting, the Board was re-organized with the following officers either installed or retained: Ivan Martin-President, Sandy Bulcher-Vice President, Dave Bulcher-Treasurer, and Anne Fredericks-Secretary. Joined by board members Amy Jones and Karen Dolins, we focused our discussion on future directions and long range planning for the MSUD Family Support Group. We highlighted the following goals:

- Become more active and more visible in the genetic disease world
- Improve the efficiency of our communication (see Editor's Note)
- Investigate potential research projects to support
- Investigate the feasibility of helping other countries with a significant MSUD population set up their own support groups

Please contact us if you have any suggestions for the Board and how we could serve you better. I'm looking forward to seeing you next year at the Symposium. §



By Katie Haley

Cambrooke Therapeutics continues to grow, innovate and broaden the spectrum of products to help improve the lives of individuals with Inborn Errors of Metabolism. These new products include medical formulas for five metabolic disorders, one which is MSUD.

Cambrooke Therapeutics is the first to offer a family of ready to drink nutritionally complete formulas for inborn errors of metabolism: Vilactin AA Plus for MSUD, provides for a patient's daily protein needs **in a new format and with unique benefits.**

Many amino acid ready to drink formulas for a condition like MSUD are harsh, have a high acid taste that lingers well after being consumed. Vilactin AA Plus formula overcomes this problem to provide a mild, low-acid flavor. It also contains essential fatty acids and DHA to support brain and eye development, support bone health with an optimized Bone Health Blend to help build and maintain healthy bones, aid digestive health with specially selected pre-biotic fiber, contain 20 grams protein equivalent in each convenient ready to drink carton, and have an all-natural berry flavor free of all artificial flavors and colors.

Patients who drink Vilactin AA Plus will find that the formula taste great and feels milder than other ready-to-drink amino acid based formulas. In addition to the taste and texture benefits, the unique low acid formulation may be gentler on digestion and oral health compared to the more highly acidic amino acid based formulas currently available. Vilactin AA Plus is convenient in a ready to drink container for all those on the go occasions and per customer request has no artificial flavor or coloring.



The low protein food line also continues to grow with five new products so far in 2015! New products include Sea Salt & Sweet Chili Tortilla chips, Cheddar Wizard (a low protein cheese dip), Pea-Not Butter (a low protein peanut butter) & Instant Soup in chicken & beef flavors- great for the colder months coming up!

For more information, to request a sample of Vilactin AA Plus, and to learn about the upcoming low-protein food discount specials, call toll-free (866) 456-9776 or visit our website at www.cambrooketherapeutics.com. §

Home Monitoring of Branched Chain Amino Acids (BCAA) Blood Concentrations

By Patricia Hall, PhD, FACMG; Rani H Singh, PhD, RD, LD. Emory University, Department of Human Genetics

Dietary monitoring with amino acid analysis is crucial for management of many inborn errors of metabolism. The gold standard for this type of monitoring is plasma amino acid analysis, which offers quantitative results for more than 20 amino acids. Plasma analysis requires a blood draw with its associated costs, and often has a list price of over \$100. Home monitoring using dried blood spots collected on filter paper (similar to what is used in newborn screening) can provide accurate results for a selected subset of amino acids important for a selected disorder, such as maple syrup urine disease (MSUD). This type of sample can be collected at home, and sent to the testing laboratory by regular mail.

The Biochemical Genetics Laboratory at EGL Genetic Diagnostics, LLC provides filter paper monitoring designed specifically for MSUD and phenylketonuria. Our MSUD filter paper assay provides quantitative values for valine, leucine, isoleucine and allo isoleucine, along with reference ranges, and a comparison to a targeted therapeutic range for leucine. Testing is done using liquid chromatog-



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raphy and tandem mass spectrometry. This assay is performed weekly and results are reported back to the ordering provider by fax. Turn-around time is seven days. Additional information about this assay can be found on our webpage (<http://geneticslab.emory.edu/tests/BMSUD>). For the specimen, we require at least one completely filled and saturated circle on a standard filter paper card. Requisition forms are available on our website, and can be customized upon request. The tests are ordered through a clinician and no direct consumer testing is available.

Our team's observations and feedback from the patients indicate that it fulfills a great gap to improve adherence to treatment. Our perspective indicates that patients receive the balanced and frequent nutrition therapy necessary to achieve optimal health and quality of life while remaining independent and comfortable in their own homes for most parts and yet connected to their clinicians. Frequent amino acid monitoring by this method in the outpatient setting along with proper diet analysis and management contributes significantly to improved outcomes. Nutrition management guideline for maple syrup urine disease including the monitoring section based on an evidence- and consensus-based approach are now available at Southeast Regional Genetics Collaborative (SERC) and Genetics Metabolic Dietitians International (GMDI). For diet analysis you should contact your clinic dietitian. §

https://southeastgenetics.org/ngp/guidelines_msud.php



Projects Funded by the MSUD Family Support Group



By Sandy Bulcher,
VP MSUD Family Support Group

Over the years, the MSUD Family Support Group has been actively involved in improving the lives of individuals affected with MSUD and their families by funding projects proposed by clinicians and researchers. The initial request for funds came in 2000 from Emory University Medical Genetics. Our organization paid for the development and publication of the MSUD Food List, a pocket-size guidebook with nutritional information for many common foods in the MSUD diet. The "little purple book" has proven to be invaluable for many families.



In 2003 the MSUD Board was approached by Dr. Harbhajan Paul and asked to fund the work he and his colleagues were doing at the University of Pittsburgh to develop an animal model with MSUD. After reviewing the research proposal, the support group ambitiously committed \$48,000 to this project. Our members came together and successfully raised the funds necessary to meet our financial commitment. The investment definitely paid off as the mice developed by the team are being used today by several labs looking for alternative treatments for MSUD.

A few years later, MSUD board members traveled to Winston-Salem, NC and met with Dr. Susan Hutson and her team at Wake Forest. The researchers presented their plan to develop an MSUD mouse model to better understand the effects of MSUD on the central nervous system and body metabolism. The board agreed to fund the research project and again our members supported the project financially. Dr. Hutson's work continues now at Virginia Tech.

At a previous symposium, MSUD parents expressed concern about the psychosocial effects of MSUD and an interest in research to better understand this issue. Fortunately, Dr. Wendy Packman and Dr. Indira Mehta from California shared our concerns and proposed a study to examine the psychosocial issues. The organization assisted financially with the project and the results were published in the *Journal of Genetic Counseling* titled "Young Adults with MSUD and Their Transition to Adulthood: Psychosocial Issues." (<http://www.ncbi.nlm.nih.gov/pubmed/22350623>)

In 2011, another researcher, Dr. William Zinnanti, reached out to our organization. Board members met in Columbus, Ohio and listened to a presentation by Dr. Zinnanti. His plans involved testing new pharmacologic treatments for MSUD, specifically Gabapentin and norleucine. After consulting with our medical advisors, the board decided to fund the project which is ongoing.

For several years, dietitians from the Genetic Metabolic Dietitians International (GMDI) and clinicians from the Southeast Regional Genetics Collaborative (SERC) worked together and developed nutritional guidelines for several metabolic disorders, including MSUD. These guidelines are used by metabolic professionals to improve care and treatment. The GMDI workgroup members felt that it was important to meet face to face to evaluate provider and patient materials based on the MSUD guidelines and requested funds to assist with meeting costs.



(Projects cont. from page 17)

The MSUD organization funded that meeting in Raleigh, NC which included several GMDI members and a representative from the MSUD Family Support Group.

In 2014, the MSUD board was approached by Dr. Gerald Downes from the University of Massachusetts- Amherst. He expressed a need for funds to establish zebrafish models for different types of MSUD. The goal is to use the zebrafish to search for new drugs to treat MSUD. The board was interested in his project and funded his work which continues (see below for an update of Dr. Downes' research).

Lastly, the organization provided funds for the development of NBS Connect, which is an internet-based support network for parents and individuals with inborn errors of metabolism. The site is managed

by staff from Emory University Department of Human Genetics. Check out the site at NBSCONNECT.ORG and take advantage of the work of these dedicated professionals.



The MSUD Family Support Group is an active organization eager to improve the lives of those with MSUD through new and improved treatments. We would not have been able to fund these projects without the generous donations of time and money from our members. We are grateful to all of our members who fundraised or personally donated to these projects. We are especially grateful to the Scott C Foster Fund and the MSUD Research Foundation. §

Zebrafish Research Continues



As noted in Sandy Bulcher's review of research supported by our group, we provided funding to Dr. Gerald Downes at the University of Massachusetts, Amherst for his work exploring the neurological consequences of BCAA toxicity in zebrafish.

In MSUD, a mutation in any one of the four genes that encode the Branched-Chain alpha-Ketoacid Dehydrogenase (BCKD) complex, the key enzyme in the metabolism of the branched-chain amino acids, leads to a buildup of these amino acids with profound neurological consequences including seizures, coma, cerebral edema (swelling of the brain), and death. How this occurs is not well understood, and we look to animal models to understand these processes.

Dr. Downes and his team developed a zebrafish model of MSUD, particularly useful because the embryos are transparent and are ready for study after

only 4 days of incubation. They expected to observe an abnormal swimming pattern in those zebrafish embryos in which the BCKD gene was disrupted. They did not find this, a result which they attributed to an inadequate dosage of the chemical used to disrupt the gene.

Dr. Downes reports that new and very exciting gene-editing technology has now emerged which side-steps the dosage problem inherent in their previous experiments. It is now very possible to quickly and cheaply mutate target zebrafish genes to perform experiments. They are moving ahead, using this gene-editing strategy to investigate how branched-chain amino metabolism effects nervous system development and function. He also plans to expose the zebrafish to thousands of different chemical compounds and evaluate the impact they have on brain function, in the hopes of identifying substances which may be useful in preventing the neurological damage which occurs with elevated levels of BCAAs. Once they complete their initial experiments, they plan to submit a grant proposal to the National Institutes of Health.

We will continue to follow Dr. Downes' research with interest. §



Many thanks to *Dana Angelo White* for submitting recipes!

See more at:
<http://danawhitenutrition.com/recipes/>

Our readers appreciate sharing in any tasty recipes you have found or developed, so please send them in!

Curry-Roasted Acorn Squash

Here's a healthy side dish featuring a seasonal delight. It's filled with cell-protecting antioxidants and fiber. Serves 8.

Ingredients:

- 2 medium acorn squash, seeded and quartered
- 2 tablespoons olive oil
- 1/2 teaspoon kosher salt
- 2 teaspoons curry powder

Directions:

Preheat oven to 425-degrees F. Place acorn squash skin side down on a sheet pan. Drizzle with olive oil and sprinkle with salt and curry powder. Roast for 20 to 25 minutes until tender.

Nutrition Info per serving:

Calories: 75; Total Fat: 4 grams; Saturated Fat: 1 gram; Total Carbohydrate: 12 grams; Protein: 1 gram (Leucine: 50mg; Isoleucine: 30mg; Valine: 40mg); Sodium: 323 milligrams; Cholesterol: 0 milligrams; Fiber: 2 grams.



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Add gel or express to apple juice. Stir in coffee creamer. Top with a dash of cinnamon and enjoy!

Nutrients	Protein Equivalent	Natural Protein	Phenylalanine	Leucine	Calories
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gel™	10 g	0.2 g	8 mg	14 mg	194 kcal
express15™	15 g	0.2 g	8 mg	14 mg	187 kcal
express20™	20 g	0.2 g	8 mg	14 mg	212 kcal

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Resource Persons:

Organizational information, printed material or addition to our mailing list:

Sandy Bulcher

Vice President
Powell, Ohio
740-972-5619
sandybulcher@gmail.com

Donations:

Dave Bulcher

Treasurer
Powell, Ohio
740-972-5618
davebulcher@gmail.com

Legislative & Education:

Marcia Hubbard

Corresponding Secretary
Cedar Hill, Missouri
314-277-8168
marciashubbard68@gmail.com

Inquiries in Spanish:

Vanessa Funes (MSUD adult)

Boston, Massachusetts
508-596-0672
mamilindafunes@live.com

Newsletter Editor:

Karen R. Dolins, Ed.D, R.D.

Newsletter Editor
Scarsdale, New York
914-723-5458
karen.dolins@yahoo.com

Advocacy:

Jordann Coleman

Advocacy Chair
Concord, CA
925-349-4601
coleman.jordann@gmail.com

Medical Advisors:**Holmes Morton, M.D.**

Clinic for Special Children, Inc.
P.O. Box 128
Strasburg, PA 17579
717-687-9407
Fax: 717-687-9237
clinicforspecialchildren.org

Melissa Wasserstein, M.D.

Director Program for Inherited Metabolic Diseases
Associate Professor
Department of Genetics and Genomic Sciences
Mount Sinai School of Medicine
New York, NY 10029
212-241-2478
Fax: 212-860-3316

Susan C. Winter, M.D.

Director medical Genetics/ Metabolism
Valley Children's Hospital
9300 Valley Children's Place
Madera, CA 93638
559-353-6400
Fax: 559-353-7213
winter2571@aol.com

Neil R. M. Buist, M.D.

Professor Emeritus
Pediatrics and Medical Genetics
Oregon Health & Science University
buistnrm@aol.com

Nutritional Advisors:**Rani Singh, Ph.D., R.D.**

Emory University
Division of Medical Genetics
2040 Ridgewood Dr.
Atlanta, GA 30322
404-778-8519
Fax: 404-778-8562
rsingh@genetics.emory.edu

Sandy van Calcar, Ph.D., R.D., C.D.

Child Development & Rehabilitation
Oregon Health and Science University
3181 SW Sam Jackson Rd
Portland, OR 97239
503-494-5500
vancalca@ohsu.edu

MSUD Family Support Group Board

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