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SUMMARY OF PAPER ON DIAGNOSIS AND TREATMENT OF MAPLE SYRUP DISEASE*

Details

Written by Dr. Holmes Morton and Dr. Kevin Strauss

Published: 20 July 2009

This article and the Abstract which follows, "Diagnosis and Treatment of Maple Syrup Disease: A Study of 36 persons" use this term.

Our paper summarizes experiences at the Clinic for Special Children caring for 36 neonates with classical maple syrup disease over an 11 year period. We describe an approach to care that includes diagnosis and management of the at-risk and ill neonate, general pediatric care during common intercurrent illnesses, chronic nutritional care, and in-hospital management of severe metabolic intoxication and brain edema. The effects of maple syrup disease upon the growth, development, and health of the patient are related to many interacting variables which are listed in Table 4 - *Determinants of Outcome in Patients With Maple Syrup Disease*. *(See end of article)* The medical approach to management of this biochemical disorder must consider such variables throughout the lifetime of the patient. Prevention of malnutrition and intoxication of the brain is obviously just as important for the teenager and adult as for the infant and child.

The management of the disorder during intercurrent illnesses is particularly problematic for parents and physicians. Few follow-up programs have recognized the need to routinely monitor amino acids levels and change management protocols during common illnesses. Our experience clearly shows that episodes of metabolic intoxication that require hospitalization resulted from the stress of intercurrent infections. Equally important, minor illnesses commonly cause increases in blood leucine concentrations and imbalances among the other essential neutral amino acids that compete with leucine for entry into the brain. Such imbalances persist for long periods of time if adjustments in therapy are not made to correct these abnormalities. Chronic deficiencies of valine and tyrosine are particularly common problems in patients with maple syrup disease.

Brain edema remains the most dangerous problem caused by maple syrup disease. It appears to us that there are three phases of brain edema in an ill patient with maple syrup disease. First, there is focal water accumulation in deep gray matter, which is readily seen by brain MRI, and dysfunction of these deep brain ganglia correlates with neurological findings and changes in behavior. Second, diffuse swelling of the brain develops and is seen clinically as somnolence, stupor or coma. This phase of general brain swelling is not well seen by MRI, as is true for early diffuse edema in patients with diabetic coma, hyperammonemia, and hypernatremic dehydration. Third, as the brain volume increases to more than 5-7% of its initial volume, the brain is pressed against the base of the skull, blood flow is interrupted in specific arteries causing focal ischemic strokes, then rapid swelling due to injury and diffuse ischemia, venous congestion, generalized loss of blood flow and brain death.

We have known for several years that brain edema worsens rapidly in association with rapid decreases in serum sodium concentration and osmolarity. Since the submission of this manuscript we have learned that these decreases in serum osmolarity and generalized brain swelling itself may be the result of high levels of a brain hormone called *vasopressin*.

Two effects of this brain hormone are familiar to all of us - thirst and a concentrated urine. Vasopressin is a hormone that normally protects against dehydration and shock. Vasopressin not only allows the kidneys to hold onto water, it also normally prevents excessive shrinkage of the brain by stimulating the uptake of sodium and water by a diffuse network of cells called *astrocytes*. Decreases in blood pressure, vomiting, dehydration, high serum sodium, glucose, or urea concentrations (all of which cause increases in serum osmolarity) provoke release of vasopressin by the brain. In the setting of increased blood and brain leucine, hyperosmolar dehydration and the associated prolonged increases in vasopressin become risk factors for the excessive and abnormal uptake of sodium and water by the brain and the development of critical brain edema. Patients at highest risk for brain edema are those who present with advanced signs of leucine intoxication including recurrent vomiting in the setting of dehydration, high serum osmolarity, and who have intense thirst caused by high vasopressin levels. Studies are underway at the Clinic and Lancaster General Hospital using neuro-imaging techniques and endocrinologic monitoring to better understand how to manage such patients to prevent progression to critical edema. We expect such studies will help explain and prevent acute brain swelling associated with maple syrup disease and several different biochemical disorders.

** Dr. Morton prefers to call MSUD maple syrup disease.*

DIAGNOSIS AND TREATMENT OF MAPLE SYRUP DISEASE: A STUDY OF 36 PATIENTS

Details

Written by D. Holmes Morton, MD; Kevin A. Strauss, MD; Donna L. Robinson, CRNP; Erik G. Puffenberger, PhD; and Richard I. Kelly, MD, PhD

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Abstract

Goal: To evaluate an approach to the diagnosis and treatment of maple syrup disease (MSD).

Methods: Family histories and molecular testing for the Y393N mutation of the E1a subunit of the branched-chain a-ketoacid dehydrogenase allow us to identify infants who were at high risk for MSD. Amino acid concentrations were measured in blood specimens from these at-risk infants between 12 and 24 hours of age. An additional 18 infants with MSD were diagnosed between 4 and 16 days of age because of metabolic illness.

A treatment protocol for MSD was designed to 1) inhibit endogenous protein catabolism, 2) sustain protein synthesis, 3) prevent deficiencies of essential amino acids, and 4) maintain normal serum osmolarity. Our protocol emphasizes the enhancement of protein anabolism and dietary correction of imbalances in plasma amino acids rather than removal of leucine by dialysis or hemofiltration. During acute illnesses, the rate of decrease of the plasma leucine level was monitored as an index of net protein synthesis or degradation. The treatment protocol for acute illnesses includes the use of mannitol, furosemide, and hypertonic saline to maintain or reestablish normal serum sodium and extracellular osmolarity and thereby prevent or reverse lifethreatening cerebral edema. Similar principles were followed for both sick and well outpatient management, especially during the first year, when careful matching of branched-chain amino acid intake with rapidly changing growth rates was necessary. Branched-chain ketoacid excretion was monitored frequently at home and branched-chain amino acid levels were measured within the time of a routine clinic visit, allowing immediate diagnosis and treatment of metabolic derangements.

Results:

1. Eighteen neonates with MSD were identified in the high risk group (n=39) between 12 and 24 hours of age using amino acid analysis of plasma or whole blood collected on filter paper. The molar ratio of leucine to alanine in plasma ranged from 1.3 to 12.4, compared to a control range of 0.12 to 0.53. None of the infants identified before three days of age and managed by our treatment protocol became ill during the neonatal period, and 16 of the 18 were managed without hospitalization.
2. Using our treatment protocol, 18 additional infants who were biochemically intoxicated at the time of diagnosis recovered rapidly. In all infants, plasma leucine levels decreased to less than 400 µmol/l between 2 to 4 days after diagnosis. Rates of decrease of the plasma leucine level using a combination of enteral and parenteral nutrition were consistently higher than those reported

for dialysis or hemoperfusion. Prevention of acute isoleucine, valine, and other plasma amino acid deficiencies by appropriate supplements allowed a sustained decrease of plasma leucine levels to the therapeutic range of 100 to 300 µmol/l, at which point dietary leucine was introduced.

3. Follow-up of the 36 infants over more than 219 patient years showed that, although common infections frequently cause loss of metabolic control, the overall rate of hospitalization after the neonatal period was only 0.56 days per patient per year of follow- up, and developmental outcomes were uniformly good. Four patients developed life-threatening cerebral edema as a consequence of metabolic intoxication induced by infection, but all recovered. These four patients each showed evidence that acutely decreased serum sodium concentration and decreased serum osmolarity were associated with rapid progression of cerebral edema during their acute illnesses.

Conclusions: Classical MSD can be managed to allow a benign neonatal course, normal growth and development, and low hospitalization rates. However, neurological function may deteriorate rapidly at any age because of metabolic intoxication provoked by common infections and injuries. Effective management of the complex pathophysiology of this biochemical disorder requires integrated management of general medical care and nutrition, as well as control of several variables that influence endogenous protein anabolism and catabolism, plasma amino acid concentrations, and serum osmolarity.

This paper is dedicated to children with maple syrup disease and their parents - *from your suffering we must learn*, and to Halvor Christensen, Ph.D. who in 1949 first observed that high leucine concentrations disturbed the rate of uptake and export of amino acids by tissues. - *hm*

Table 4. Determinants of Outcome in Patients with Maple Syrup Disease

Neonatal

- Time required to reduce plasma and tissue leucine levels to normal
- Prevention of hyponatremia and vascular compression by critical cerebral edema
- Prevention of prolonged, severe brain essential amino acid deficiency
- Age at diagnosis
- Degree of illness at diagnosis

Dietary control when well

- Methods for home monitoring of metabolic control
- Adjustments for changes in leucine tolerance as a function of growth velocity
- Prevention of systemic and brain essential amino acid deficiency
- Prevention of nutritional deficiencies caused by dependence upon artificial foods

Control of catabolism during intercurrent illnesses or stress

- Methods for local or home monitoring of metabolic status
- Effective sick-day management during common infections and after immunizations
- Timely treatment of common infections
- Prevention of exercise-induced metabolic decompensation
- Control of metabolic decompensation caused by cold, heat, or psychological stresses
- Prevention of central nervous system water intoxication

Acute medical care

- Access to metabolically-informed medical care during minor illnesses
- Effective care in hospital during acute illnesses and after injuries or surgery
- Inhibition of protein catabolism and support of protein synthesis to lower plasma leucine
- Prevention of peripheral and brain essential amino acid deficiencies
- Control of uncommon infections: immune dysfunction, central line infections
- Prevention or effective management of pancreatitis
- Prevention of water and sodium derangements and regional brain edema
- Prevention of vascular injuries caused by critical cerebral edema

The complete article, "Diagnosis and Treatment of Maple Syrup Disease: A Study of 36 Patients" as printed in Pediatrics *is 10 pages describing the treatment of classic MSUD. The article as published can be viewed on Pediatrics' web site: www.pediatrics.org*
Dr. Holmes Morton, Dr. Kevin Strauss, Donna Robinson and Dr. Erik Puffenberger, authors of the above article, are from the Clinic For Special Children, Strasburg, Pennsylvania. See following article on The Clinic for Special Children.

Editor's Note:
Dr. Morton prefers to leave the word "urine" out of MSUD. He calls the disorder "maple syrup disease." The name "maple syrup urine disease" has been used since the disorder was identified in the 1950s. MSUD calls attention to the odor in the urine which is so often a factor in diagnosing the disorder. To avoid confusion this *Newsletter* will continue to use MSUD. - Jb

The Clinic For Special Children
This unique non-profit Clinic was founded in 1989. Dr. and Mrs. Morton had strong community support in their efforts to provide affordable healthcare for this large community of Amish and Mennonites in Lancaster County, Pennsylvania. Most of these conservative church groups do not carry insurance nor do they use government programs. The Amish families have a high incidence of glutaric aciduria (GA1) and Mennonite families have a high incidence of classic maple syrup urine disease (named Mennonite Classic because of the one single mutation involved). In 1990 many local families helped "raise" the first building for the Clinic in the traditional Amish "barn-raising" style.

The original objective of the Clinic was to treat children with MSUD and GA1 in the surrounding community. However, the need for a similar approach to care for these and other disorders in other locations has increased the demand for clinic services far beyond the original plans. Expanding in size and services, the Clinic has served families from other areas and treated many disorders. Clinic services now include newborn screening and carrier testing for fifteen genetic disorders. The Clinic is also pursuing genetic research in its modern laboratory.

Thirty to forty percent of the Clinic's yearly operating expense is met by funds from three auctions held annually. These auctions and other contributions support the Clinic so families are not unduly burdened with high medical costs.

The auctions are a feast of the finest in Pennsylvania Dutch crafts, quilts, food, handcrafted furniture, items as big as sheds, and many speciality items - all donated. Delicious home-

baked items and food stands draw crowds. The huge auctions usually have three or more auction rings going from eight in the morning until late afternoon. For a delightful time and money well spent, include one of these auctions in your summer travels:

- Shippensburg Auction, Shippensburg, Pennsylvania
- Blair County Auction, north of Woodbury, Pennsylvania
- Lancaster County Auction, Leola , Pennsylvaniañ Always held the third Saturday of September

For more information on the Clinic or the auctions, call 717-687-9407 or check the Clinic's new web site: www.ClinicForSpecialChildren.com
- The Editor

FEATURED FAMILIES - THE VILLELA STORY

Details

Written by Ruth Villela

Published: 20 July 2009

My husband and I were just 20 years old when we got married. My husband Paulo earned a degree in Agricultural Engineering. He was pursuing his dream of managing his family estate. I was pursuing my degree in special education. Being high school sweethearts, it seemed that our lives were complete. We grew up in privileged families in Brazil so our futures were set.

On August 16, 1980, I gave birth to a healthy boy, Gabriel, and life was so beautiful. Two weeks later, my baby showed some irritability and his appetite deteriorated. My mom was the first one to notice something strange; he was having convulsions. We rushed to a hospital. A great doctor in Rio de Janeiro, Dr. Pedro Solberg, came and diagnosed him with MSUD. A week later, we lost a part of us, our baby died.

At that time, my understanding of this disease was very limited. We knew that children with MSUD need a special diet. We had no idea about what the treatment would entail. Months later, I found out I was pregnant again. This time I went to Boston to have an amniocentesis done by Dr. Vivian Shih. Because of my difficulty with the language at the time, I had to always ask people to talk to the doctors for me. Three months later, we found out this baby had MSUD too. That is when our lives changed completely.

Dr. Vivian Shih told us to contact Dr. Selma Snyderman in New York. Talking to Dr. Snyderman, we found out that we would have to come to New York. She was afraid that in Brazil they would not be able to administer the special formula. My husband was finishing his university studies, so my mother and I came to New York in July 1981.

Bernardo was born August 27, 1981, a beautiful, healthy boy. He stayed in Bellevue hospital for three weeks. Some moments were very hard, but he did great. Afterwards, we stayed in New York until he was three months old. Then we went back to Brazil thinking we could handle the diet ourselves. However, in my country, we were not able to have the amino acid levels tested. Therefore, we had to send blood to the United States every time.

This always took long and by the time we got the results, he would be hospitalized.
The way we monitored him was with DNPH. Therefore, my doctor in Rio thought it would be a good idea to go back to New York and learn more about MSUD, especially about Bernardo's food. He was almost 11 months old, and he would just have vegetable soup. I guess that is why today he cannot stand to see soup in front of him. We went to the U.S., thinking of staying six months so we could learn everything. Then we could finally return to reside in Brazil to live our normal lives again.

The more we learned about MSUD, the more scared we became. So every year, we dreamed of the day we could go back to our home. However, year after year passed and talking to doctor Snyderman about the reality of Brazil made us stay. Bernardo was hospitalized a lot and every time was very difficult for us. We did not have the support of our family, and Paulo was always working. He was the wage-earner, so I was always alone. Seeing my son suffer so much was almost unbearable to me at times.

Years passed and Bernardo was doing great in school. I got pregnant again. This time I gave birth to a beautiful girl who we named Diane. She just stayed six days in the hospital. With this baby, I did not feel so overwhelmed since I had more experience with MSUD. Diane was a fighter since she was a tiny baby. She had some complications as an infant, but is doing great now. School was always a hassle for her, but she is very determined and always gives her best.

My kids had a lot of problems when they were young with behavior issues that we did not know were MSUD related. Now reading the e-mails from parents with young kids in the Support Group, it is so clear to me. I can see the blessing this group is to those in it. Most of my friends did not understand my children at all. The more people can be educated about any condition, the better it will be for everyone.

We have one more child, Felipe. He does not have MSUD. Felipe is a great child, but it is hard for him to understand why: when things happen to his siblings health-wise, we jump, and with him, we are more relaxed. He loves everything I cook for his brother and sister.

A lot happened to us these last few years. I must mention that during the most important and difficult times we have had, you MSUD families were a support to us. My husband has a degree in engineering, but in New York he was obligated to grab any position to support our family. So he started working as a waiter in Staten Island in a local restaurant.

After years of very hard work, in 1996, he arrived in Windows on the World, one of the most famous and beautiful places we ever saw. There Paulo found his future for the first time in the restaurant business. Soon he was promoted to captain, and then, after that, he became a Sommelier. Windows became a family to him and to us. Windows was the first place where Paulo felt comfortable working in a job that was outside of his field of study. Bernardo worked there, too, as a steward in the wine cellar. Our family enjoyed so many great times, so many celebrations. Certainly the greatest feeling is when our kids who have such a strict diet can enjoy great food made by an unbelievable chef like Michael Lomonaco. The food was made with love for them. The view from the restaurant was something "out of this world." We were there in May, 2001 with my mother and family.

The day of the attack on the World Trade Center, we did not know what was going on. Paulo always left at 7:30 a.m. to take the kids to school and then go directly to work. However, THAT TUESDAY was Felipe's birthday. So my husband stayed home to have lunch with him. The phone would not stop ringing. When I answered, I heard my friend crying hysterically, asking me where Paulo was. That is when we knew something horrible must have happened. We turned on our TV, and we could not believe it. Paulo's building was the first one to be hit.

Paulo immediately tried to call his friends, but already none of the phone lines were working. There were 80 people working at Windows that morning. The day before, the manager asked Paulo if he could come to work on the breakfast, because they needed help. And Paulo said no. He never said no before, because we always needed extra money. Our whole family, even today yet, prays at mass to thank God for saving my husband that day. My husband's friends have been coming to visit, and that is all we talk about. It's a way of dealing with all the feelings inside us. Windows will always be in our memory, as the top of the world. I would like to take this opportunity to thank you again for all the help and support the MSUD group gave to us.

I would not want to finish this without talking a little about Dr. Morton. We attended the last MSUD Symposium (2000). For us, it was the first time, and for me it was very important. For the first time, I was able to understand millions of things about this disease that before were completely incomprehensible to a layman like me. Dr. Morton was able to take away many fears that have been inside of me. I learned all the new ways of treatment. After living through so much as a mother of two children with classic MSUD, I have also come to the realization that their mental health and well-being is so critical to their physical health. Certainly, as parents we cannot treat our kids medically, but we know them better than anyone. I always promise my children that I would do anything within my power to minimize their pain, and that some day their treatment would be less overwhelming and traumatic.

We'll always be grateful for everything Dr. Snyderman and her colleague Dr. Sansaricq did for us, and we only hope that all the metabolic specialists will work together to help the children cope with their illness. Now my kids are in the care of Dr. Morton, and they are doing really well. Bernardo is now 20 and in his junior year at Fairleigh Dickinson University. He is majoring in film-making. He was an honor student last semester. Diane is 15 and finishing junior high. Felipe is 11 years old and just started the sixth grade.

In closing, I realize how blessed my children are to receive adequate treatment that gives them the opportunity to lead a normal life. I will always be grateful for all those who helped my children grow up to be two amazing and incredible people.
God Bless you All!
Love Always, Ruth Villela

FEATURED FAMILIES - A MOTHER'S STORY

Details

Written by Lucie Ellsberry

Published: 20 July 2009

It was a beautiful morning September 6, 1996 when Jeremiah Daniel Ellsberry was born. He weighed 7 lbs. 11 oz. - all boy. Everything went well. He was treated for low blood sugar and discharged three days later. About the fourth day, we noticed he didn't want to drink from my breast, so I gave him formula in a bottle. It only worked for a while. That day he had his first checkup and the doctor just gave me medicine to wet his eye ducts, said he had colic, and sent us home.

By now I was concerned because Jeremiah wouldn't stop crying. So we decided to take him to the emergency room. We were treated as if we were "overreacting parents with a firstborn." At that time, I had two daughters (Frances 17 and Vanessa 14) and my husband had one son (CJ 6). So we weren't first-time parents. In the ER, several tests were done including a urine test. It was hard to complete the tests, including one for ketones, because Jeremiah was not able to take in any liquids. The hospital sent us home saying it was only colic.

In the next 24 hours, he only took 2 oz. of formula. Then I knew something was wrong. He kicked and cried most of the fifth day. That evening we debated about taking him back to the emergency room because of how they made us feel doing during our first visit. We wanted to make sure we were not overreacting. We decided our son Jeremiah means more to us than what the hospital thinks of us. So off to the emergency room one more time.

A spinal test taken in the ER came back negative. Thank God! So what was the problem? While we sat and waited for other test results, our son was having screaming spells every so many minutes and would sleep between these episodes. Later we learned they were seizures. We told the doctors we were not taking Jeremiah home until they could find out

what was wrong with our son. Because we had HMO insurance, they had to have a reason to admit him. So we just stood there, waiting for help.

We started calling everyone from church and our families to put Jeremiah on the prayer chain. Everything seemed so unreal, like I was going to wake up from a bad dream. I started thinking about the Scripture that says He will not give us more than we can handle.

In the emergency room, there was a nurse who had been there the night before. She came in our room and asked what was going on. We explained, and she stood there watching Jeremiah for a couple of hours. We did not know her shift was over, but she was determined to find out what was wrong. I believe this was God's doing again - God bless her. She saw the pattern of his outbursts and requested that he be admitted for more testing. By then it was the sixth day and nothing was happening. Jeremiah was deteriorating in front of us and there was nothing we could do but pray. We felt so helpless! This is the time we needed to trust in the Lord.

Our son looked as if he was resting peacefully. By this time, it seemed everyone from our church and family was there for support and prayer. When I remember this time, I thank God for that support. Having a strong foundation in the Lord helps. Amen.

The doctors could not find what was wrong. They asked us to make a choice between continuing with more tests or transporting him to Long Beach Children's Hospital where they had specialists for babies. I shouted, "What are you waiting for!" While Jeremiah was being transported, he fell into a coma. That was real scary - a feeling that I could never describe, but this was reality.

When he arrived at the hospital, Jeremiah was put in intensive care with all the newborns. He was put in isolation because he had been taken home for a couple of days. I look at it as God giving him his own private room. Visitors were allowed in as long as they scrubbed up. So he could be prayed over and was anointed by our pastor and church leadership. Many others from all over the world were praying for Jeremiah, and we knew God had his hands upon our son.

Jeremiah looked so big in his incubator compared to all the other infants in ICU. We thought of what all the other parents were going through. It gave us an opportunity to minister and witness to them. Our friends and family came by during all hours of the day, bringing food or taking us out to get away for a while. We thank God for them. They kept us from going insane.

All I can remember of this time is the doctors asking us a lot of questions. It was on the tenth day, a special doctor (another of God's angels) asked our daughters if they could recall anything different about their brother. They remembered that Jeremiah never smelled like a "fresh smelling baby," even after a bath.

Then the doctor found Jeremiah's ketones elevated and started treating him for MSUD, pumping him with calories. The doctors and nurses were moving fast. They needed our authorization to put a thin line in his chest, so the fluids could go in faster and not get clogged. That was a hard decision to make.

The doctors said this could be a long waiting period, and they didn't know what to expect since he was the first child ever treated there for MSUD. First we had to wait for Jeremiah to come out of the coma, and then see how much damage he had sustained while in a coma. We tried not to lose hope, but it was still hard to hear those words.

We were alone one night in Jeremiah's room, on our knees, praying to God. God put in our hearts that if He gave us our son, He could take him from us at anytime. We needed to accept this. We had so much peace after that. We started concentrating on going around doing God's work and praying for the other children and their families. That kept us from being consumed by our own situation. Then we were able to use this time for God's glory.

Now that we knew what our son had, what was MSUD? The name itself was funny. When the doctors explained the disease and how rare it was, it was a wake-up call. They gave us the worst outcome. He might not walk, and if he did walk, he would be a skinny kid who would not be strong enough to play sports. I remember looking at his dad's face - speechless. I felt like I was on a roller-coaster ride. We were thankful we knew what was wrong and then had moments when we would fall apart wondering how are we going to take care of our son. We hung on daily to this Scripture (Philippians 4:13), "I can do all things through Christ who strengthens me." Some days my husband would be the strong one, other days I would be the strong one. Then there were nights when we both would break down and cry out to God for strength to get through another night.

When Jeremiah opened his eyes and smiled again, we could not contain our joy. It was like our son was born all over again. We knew it would be a hard road ahead of us, but he was out of his coma and that's all that mattered at that time. "Nothing is impossible with God" Luke 1:37. Amen.

We still spent every night in the hospital, until one day a sweet lady dressed as a nurse came to visit Jeremiah. She convinced us to go home for the night and promised to check in on our son during the night. She made us feel at peace about going home for the first time since our son was in the hospital. The next morning, we could not wait to see Jeremiah. We ran into that special nurse in another section of the hospital, and she told us our son was fine all night long. She gave us a pendant with a pair of footprints and a Scripture verse, Jeremiah 1:5, "Before I formed you in the womb, I knew you, before you were born I set you apart, I appointed you as a prophet to the nations." She wanted to make sure I placed it in Jeremiah's crib in the hospital. We looked for her later to thank her, and she was nowhere to be found. No one knew who she was. I believe she was another angel sent from God.

Our son was improving and getting stronger. He was fed through a gastric tube until he learned how to suck again. We had a lot of support from the hospital staff. It was a real scary thought that this hospital had never treated anyone with MSUD before, so we knew we had to do a lot of research on our own. I praise God for the MSUD Family Support Group. I remember reading about what happens when a baby is not diagnosed within 10 days. Like I said, God had His hand upon my son.

The hospital tried to prepare us to care for our son at home. Everyone who would be caring for him had to take CPR classes. After 30 days in the hospital, it was time to take our Jeremiah home. I was so scared. Could I take good care of all his needs? I knew I couldn't

go back to work right away and leave someone with this responsibility. At first his father prepared his formula every day until I was comfortable doing it myself.

Then came the weekly visits to the doctor's office for drawing blood. The visits changed to every two weeks, then monthly. When Jeremiah was ill, he went straight to the hospital for a couple of days at a time. It was hard to see him go through all this.

Then I had to deal with my husband's battling substance abuse. This started when our son was around six months old. It started with my husband being away for a day, then weeks, then for months at a time. It really took a toll on me and on my relationship with God. But I hung with His promises that He would never leave us or forsake us. I tried not to lean on my understanding, but on His. I eventually went back to work and had a good babysitter who I knew I could trust with my son. She was a wonderful blessing.

As time went on, my son was in and out of the hospital around three to four times a year. Last year, 2001, he was only in once; the last time in December. Jeremiah even went through a major ordeal when he was abducted by his father and was off his formula for four days in May 2001. He was found in good health, which was a miracle in itself. Doctors are still puzzled by the outcome. I know why nothing happened to him, even though he was in a very dangerous place. The Blood of the Lamb protected him. God even protected my family and church family while they went into the darkness to look for my son every day until he was found. God even used a drug dealer prostitute to turn my husband in. Prayers went to God from all over for our protection and safety. This trial just brought me closer to my Savior Jesus Christ. Amen. Because of this incident, the Lord has become my son's fatherly image for right now. What better example of a father can he have? None!

Jeremiah enjoys playing baseball, and this year will play soccer. He will be starting kindergarten this September, so keep us in your prayers. He has been going to our church preschool since he was 18 months old, and they take good care of him.

I believe God has given my son a soft spirit towards people who are hurting or struggling in life. Jeremiah senses things in people and wants to pour love into them. He has been my inspiration to continue to live in spite of the struggles and obstacles in my life. We call him "Miah" for short. He loves hamburger Happy Meals from McDonald's without the meat, cheese and corn. He loves to go dirt bike riding with the Dirt Dogs from church, and his favorite place to hang out is the skate park at church. He loves to go on our church's outreaches. He encourages me to go also. He has been really blessed by the Godly men at our church who take him under their wings and spend time with him.

With the Grace of God, we have been able to get through this and will continue to stand firm in God's Word. I treat my son's disease as a challenge, and I don't allow it to consume our lives. I continue to do all the things I dreamed I would do with my son. I try not to shelter Jeremiah from anything or anyone, and by the looks of him, I think he's in good health. Thank you Lord.

I hope this article will minister and give hope to all who read it, because I give all the glory to God first. I also thank my family, church family, especially our pastors and their wives, who are not only my shepherds, but my friends. There are so many I didn't mention who have

been there for both Jeremiah and me through all of this and are still there. You know who you are, and may the Lord bless you all.

Love, Lucie Ellsberry

SHARING - MISDIAGNOSED WITH MSUD

Details

Written by Beth Mauldin

Published: 20 July 2009

In December 1999, when our son Benjamin was seven months old, he ate his first substantial protein load. Being fish-egg-dairy vegetarians, we gave him salmon. He loved it and ate a portion we later calculated to be about twenty grams of protein. About two in the morning, he became very agitated, made a high- pitched repetitive cry, stared vacantly, and was inconsolable and unresponsive. My husband and I almost took him to the hospital before he settled down, became responsive, and went back to sleep. In the morning, we found a dried urine spot on his pajamas that smelled oddly like maple syrup. I first suspected that he might be diabetic, but on a whim I checked the Merck Manual's index for maple syrup. Much to my astonishment, I found a listing for maple syrup urine disease and read about how effected persons have an inability to metabolize particular amino acids. Believing there could be a connection between our terrible night and Ben's salmon dinner, I consulted the Internet for more information and then made an appointment to see our pediatrician.

After scouring through the old newsletters and general information on the MSUD Family Support Group web site, I had many questions for our doctor. She told me that it was impossible for Ben to have a metabolic disorder and look so well. According to the information I found on the web site, that was not necessarily true. My impression was that if substantive damage had not occurred, a child could appear, and actually be, well.

Once again, I turned to the web site. This time I found Dr. Susan Winter's e-mail address. I sent her a question regarding variant forms of MSUD and asked whether my son should be tested. Dr. Winter responded very quickly. Yes, he should be tested, and a plasma quantitative amino acids test would be the starting point. After a bit of arm-bending, our pediatrician ordered a test which came back mildly abnormal. (The test was inferior to the one recommended by Dr. Winter.) Dr. Winter believed the degree of elevation was inconclusive and suggested that we look for alloisoleucine.

The labs in the area had no information on how to find this marker and could not perform the test. We were then referred to the head of the pediatric metabolic and genetics department at a regional teaching hospital.

After months of waiting, in April 2000, when Ben was 11 months old, we saw the specialist and another quantitative amino acid test was ordered with a protein load.

It too came back abnormal with two times normal valine and leucine, and three times normal isoleucine. Several other amino acids were also elevated. At the bottom of the test report was an interesting notation. "In this sample, the concentrations of several unrelated amino acids were elevated. This pattern is non-specific and likely represents a dietary artifact (non-fasting sample)."

Ben was then given high doses of thiamine and another test was performed with a protein load. Similar elevations showed up along with the same notation. To me this notation suggested that the results showed that my son had eaten before the test and potentially nothing more.

After consulting with our specialist, I asked about this notation and the other elevated amino acids and my question was circumnavigated. I also asked about looking for alloisoleucine and was told this was not necessary. We were told that Ben's pattern of elevation was typical of the disorder and that no further tests were needed. I asked if there could be a problem with his liver, and the answer was no. His ears were not swabbed for the distinctive maple syrup odor. With only the results from one type of test, Ben was diagnosed as having a mild variant form of MSUD. He was placed on a two gram of protein per kilogram of body weight diet and ordered to return in a year.

I went home wondering to myself how the two gram diet was determined? How did the specialist know my son's liver was functioning properly, and how could you rely on tests that were conducted with arbitrary protein loads? Why were other amino acids elevated, and why were different ones elevated on a repeat of the same test? Did the notation really mean that Ben's amino acids were elevated simply from the food he ate?

After months of these questions nagging at me and having a specialist who was, for whatever reason, incapable of providing answers, I joined the MSUD eGroup. I was overwhelmed by the seriousness of the disorder and the degree of monitoring that was supposed to be done. I had never heard of DNPH testing. Ben was not on formula. We had no sick day plan. We had no substantive dietary counseling. Other eGroup children's blood leucine levels were monitored monthly, weekly, and even daily in some circumstances. It was clear that we were not getting quality care.

Then the breaking point came - our son started vomiting in the evening. This happened several times over a two week period and was a red flag to other MSUD parents that Ben's leucine levels were elevated. Another eGroup parent actually phoned us believing that our son's situation was potentially quite serious.

We knew we needed to see a doctor who was knowledgeable about MSUD, and, unfortunately, we were already seeing the most qualified doctor in our area. We called Dr. Holmes Morton. Even though he typically does not work with variants, Dr. Morton consulted with us over the phone. After listening to the little information I had and hearing the fact that our son's ear wax

never had the maple syrup smell, Dr. Morton suggested we come to Pennsylvania so that he could rule out MSUD as our son's problem.

I was stunned with the suggestion that Ben may *not* have the disorder that had nearly consumed me with worry for over a year. Dr. Morton suspected that Ben's problems - vomiting, irritability, restlessness, insomnia, hyperactivity, head-sensitivity, head-banging, and thin hair - stemmed from causes other than MSUD. Needless to say, we were off to Lancaster.

When we arrived at the Lancaster General Hospital, our room was waiting for us; Dr. Morton arrived shortly thereafter. We stayed overnight and several tests were performed. One test showed that Ben metabolized valine and phenylalanine (the control) at similar rates which meant that he had no trouble with valine. Next, Ben ingested several doses of leucine over several hours. His blood was checked, and there was no accumulation, which meant his body also metabolized leucine. His liver was checked, and its function was normal. We were stunned and thrilled. The conclusion: Benjamin never had any form of MSUD.

How had this misdiagnosis happened? We believe there were two primary explanations. The first was likely caused by the sheer broadness of the fields of metabolics/genetics. Many doctors may have little experience in diagnosing and treating one of the many rare disorders that fall into this category, unless of course, that particular disease is their speciality. In hindsight, we know that we should have asked our specialist how many patients with MSUD he had diagnosed and treated.

Our second explanation for the misdiagnosis is that we were not sufficiently forceful or persistent in getting clear explanations for our questions. The moment I was given a vague answer, and when it was apparent that further questions were not welcome, we should have immediately sought another doctor. Ultimately, we learned that the care and welfare of our children is a parental responsibility and parents must be their child's advocate. Never stop asking questions and make sure that you are getting substantive answers. Thankfully, we also learned that there are amazingly competent, patient doctors who are willing to help and provide complete information.

Dr. Morton and his colleague, Dr. Strauss, believe that there is a possibility that Ben has been experiencing pediatric migraines which could explain his many symptoms. He is currently under observation, and when he has greater verbal ability this diagnosis could be confirmed.

We would like to thank Dr. Susan Winter, who was instrumental in having our son tested quickly. It would likely have saved him from neurological damage if he actually had MSUD. We would also like to extend our deepest thanks to Dr. Holmes Morton, who, as many of you know, is not only a brilliant doctor but also a most generous and wonderful man.

We, on the eGroup were all concerned: Did Ben suffer any damage from being on the restricted protein diet for 15 months? In an e-mail after their visit with Dr. Morton, Beth wrote that the doctors did not think there was any permanent damage. The two gram per kilogram diet probably would have been too high had Ben had a variant form of MSUD. He was still getting

infant formula, cheese, soybeans and peanut butter - basically a vegetarian diet. He is at the top of the growth charts, and has met all the milestones for his age.

Since Beth wrote this article in Oct. 2001, she and her husband think they have discovered the cause of Ben's vomiting episodes. They believe feeding him milk along with acidic fruit causes curdling in his stomach and subsequent vomiting. Eliminating the combination has eliminated the vomiting. Ben is still a very intense boy and does not have a good appetite. But who can figure out all the behaviors of any almost three year old! Now they at least know it is not related to MSUD.

SHARING - WITH NO PRIOR EXPERIENCE

Details

Written by Marcia Hubbard

Published: 20 July 2009

With the birth of my second grandson in 1998, I was introduced to MSUD. As the day care provider for my grandsons, one with MSUD and the other with Pervasive Development Disorder (PDD), I learned firsthand the special challenges for both. Internet support groups and eGroups were my outside source of information. Messages on these groups soon made me realize the laws in Missouri were more limiting for MSUD than for PDD.

A chance meeting with our State Representative gave me insight into the possibility of changing these laws. With no prior experience, but with advice from the eGroups, I commenced a journey though the Missouri General Assembly. Through the eGroups I contacted as many persons in our state as possible. I prepared an instruction packet with pre-written letters for these persons to send to their legislators. These packets were distributed to others in the state through clinics.

Families were extremely helpful and very willing to unite. By the second year, a bill was passed that will require the insurance industry to cover low protein foods for Inherited Disorders of Amino Acids. The new law fell short of our original goal (it has a $5000 a year cap, with coverage for those up to six years of age), but it is a large step in the right direction. The support groups and eGroups will continue to be used as we pursue our goal. We united for a common goal, and for this I am thankful.

SHARING - COMMENTS FROM EGROUP MEMBERS

Details

Written by Joyce Brubacher

Published: 20 July 2009

Celeste Battle, California
The *MSUD Newsletter*, the web site and the eGroup are life-savers for the family with a child having this genetic disorder. My son Brock is 23 years old with Classic MSUD. We spent many years feeling very isolated, as if we were the only family dealing with MSUD. Then we were told about the *MSUD Newsletter* by a physician at Buffalo Children's Hospital. Life got easier knowing there were others just like us! Sharing and learning helped us survive. Now we have the web site and the MSUD eGroup to help us.

I have learned so much from communicating with others about this disorder. After all these years, I am still learning about MSUD, the effects of certain medications on the amino acid levels, gaining new ideas on managing illnesses and mood swings, etc. This group is a lifeline, a sounding board, a question and answer board filled with outstanding, objective information and true life experiences which are the best learning tools. My heartfelt thanks go to all who contribute information. I for one would not want to be without this eGroup and the *Newsletter*. They make difficult times so much easier to handle! Thanks to all of you.

Sandy Kiel, Michigan
I enjoy the eGroup because I face so many problems and ideas every day. It's like having your neighbor over for coffee to discuss your kids; only our neighbors are across the world, and our kids have very unique problems. We all share the same goal - healthy children - and want to help each other reach that goal. It's a big comfort to know there are many others struggling with the same issues I struggle with every day: formula, nutrition, food likes and dislikes, and hospitalizations. We are able to draw on each others' experiences, which is invaluable. The group is more than an exchange of information. It is support and encouragement for each other.

Nikolai Rudd, Massachusetts
What I have found to be most interesting in being part of the eGroup is the information on problems people are having, especially the older group of persons with MSUD. We seem to be having problems we had not encountered when in our teens. From those participating in this group, I've learned that we older ones experience similar symptoms. So, when I had appointments with my doctors, I was able to give them information about others who were experiencing the same problems.

As an adult, I feel we are the guinea pigs of this disease. No one really knows if other problems will arise in the future because of something lacking in our diets. It is encouraging when I read about the plight of other people and together we try to figure out what may be happening. In a sense, we are like the characters on "Dark Angel."

We are encouraged to believe that our diets are doing what they are intended to do, but are they? We need to share experiences with each other more frequently than every two years at the Symposiums. Changes are happening during those two years. Are others also finding they are becoming ill more easily? Are they having chronic back pains and other chronic problems?

I find it both encouraging and somewhat alarming that a lot of the older MSUD persons are experiencing symptoms of "anxiety disorder" as I have experienced. This is an issue that we should not take lightly, even though it is a common disorder, and may not pertain to MSUD at all. As a group, we need to examine the possible connection to MSUD so the next generation of adults will be able to prevent this problem and others.

Calling everyone to discuss problems costs more money than I can afford. So I am thankful for this group which allows each of us to freely express ourselves and even help others. My only regret is that there are not more teens/adults using the eGroup as a resource. But if any one has questions that they'd like to ask about school, sports, fitting in, etc., I'll be more than happy to help answer them as I'm sure the other adults would too. Feel free to use us as resources at the Symposium. Chances are, I'll use you too.

Monica Falconer, Alaska
After our first son was diagnosed with MSUD - a condition we had never heard of before - we felt alone, scared and insecure. But this feeling only lasted a few weeks. Soon after we came home from the hospital with our recovered son, we sat down at our computer and looked for the MSUD Support Group we had been told about at the hospital.

We wrote an introductory message to the MSUD eGroup, and, to our surprise, half an hour later we received at least four messages from families welcoming us and letting us know that they were there - somewhere in the country, maybe living far from us, but always only a computer screen away. It was an amazing feeling of support right away.

I remember that when we received those messages we felt good for the first time since we were told of our son's diagnosis. Now we know that we have families, friends, persons who are there for us with information, or to help us find the answers to all our questions, to give us the support that we all need.

We had never been told about the DNPH solution as a way to check for elevated levels of leucine. It was through the eGroup that we first heard of it. Despite our doctor's reluctance, we were determined to give it a try. We no longer have to be "in the dark" when our son's behavior changes, but can use DNPH to see if it has something to do with his elevated amino acid levels.

The MSUD group is like a second family to us. A family that we keep in contact with very frequently, a family that we think of daily, and a family that we love, appreciate and are very

proud of. For families with relatives with MSUD, we highly recommend that they join the eGroup. It's just great!

Denise Pinskey, Michigan
I love having the MSUD eGroup. It's great to ask other MSUD families questions and get a quick response. Sometimes it is very hard to explain the disease to our family and friends and get genuine understanding. When I have a question, I know everyone in the eGroup will give an honest opinion from the MSUD perspective.

Patty Swenson, Colorado
I have found the MSUD group e-mail very valuable. Even though we have been living with Classic MSUD for 31 years, there is still so much to learn. We were able to start using isoleucine and valine supplements last year as well as DNPH for the first time. So even though I am an "old-time MSUD Mom," I was new with supplements and DNPH. All of the MSUD parents in the group helped me to completely understand and use the newer tools to manage MSUD. It has been very supportive to have other parents helping when you have no one else to talk to about MSUD. I find the eGroup helpful and supportive. Thanks!

Melisa Carr, South Carolina
The MSUD eGroup has been a very big help to me in learning about MSUD. Through questions and comments made in the e-mails, I found out several things that have improved the quality of life for my child Karena who is now 17.

Karena was diagnosed with variant MSUD at the age of 15. The doctors told me it was something they reviewed in medical school, but they were told never to expect to see anyone with the disease. I went to the Internet in search of information regarding her diagnosis. I was led to the MSUD web site and have been reading ever since.

Karena was in a psychiatric hospital for severe auditory, visual and tactile hallucinations. I was told that I should put her in an institution, that I would never be able to take care of her. She was on multiple psychotropic medications. She was not able to take care of herself; she drooled constantly from side effects of the medications. She had severe tremors of her hands and stared into space most of the time unable to comprehend what was going on around her. She had an MRI done at that time to check for possible causes of her mental and physical deterioration. The MRI showed changes in the white matter of her brain. This led the doctors to do a spinal tap. The diagnosis of MSUD was revealed in the tests run on her spinal fluid.

Karena was started on the protein restricted diet and an MSUD formula. This was an extreme adjustment for her; she was no longer able to eat whatever she wanted. She hated the formula. That was a battle I dreaded three times a day, every day. She would gag and vomit as she tried to drink it. We tried every product available. She now takes the amino acid complex blend mixed in apple juice twice a day.

I had, at one point, asked the eGroup if any other children had hallucinations. Many responded that there were times when their children's levels were high that they talked about seeing objects that were not there. With this information, I began to keep a close watch on Karena's levels to see if they correlated with her hallucinations. I noticed that she only experienced hallucinations when she was sick or her levels were high.

In March, after several months of monitoring, I talked with her doctor about my observations along with the information I had gotten from the eGroup. I asked that we try taking Karena off her anti-psychotic medication. She was weaned over a four-week period.

A week after she was completely off the medication, her tremors were gone, although she was still groggy most of the time and not able to stay on task. Not too long ago, I learned through the group that valproic acid should never be given to people with MSUD. Karena was on a large dose of Depakote SR, an extended release form of valproic acid. She was always lethargic and extremely irritable. At times she would not eat well, and her levels were always low. I informed her doctor about what I had learned through the eGroup, and she agreed to try Karena off the medication. This was about six weeks ago.

Since that time, Karena is much more alert. She is able to stay on task, complete her school assignments, and is going to start attending regular classes this fall. She has been on homebound schooling for the past three years and was making no progress. The teachers had labeled her as non-educatable. They were suggesting that we give up and allow her to complete high school this year with a certificate of attendance. Now she is eligible to start working towards her diploma again, although she will start slow. It will be four more years before she will have enough credits to graduate.

I share the valuable information I obtain from the eGroup with Karena's doctors and dietician. I feel that personal experience and sharing are the best tools for learning. There is a lot to learn from one another. I am grateful to all of the participating members for sharing their knowledge and experience, and I enjoy reading the e-mails I receive.
I hope that some day I can share the type of valuable information that I have gotten from this group and make as big a difference in someone's life as they have made in ours. Thank you.

This eGroup has been very active this past year and covered many subjects. Parents ask: How do you get a child to drink the formula when they refuse? Do other children with MSUD have problems when it is hot? How do others mix their formula so it is well blended? What new low protein foods are well liked? How have others reacted to anesthesia? Many other topics have been covered and each person learns from the responses.

You can be part of this exclusive group e-mail account. Contact Emily at this e-mail address: emilytalley@mindspring.com. Ask to be added to the MSUD eGroup and be sure to tell her how you are connected to MSUD - as a parent, teen or adult with MSUD or a professional dealing with MSUD.

SHARING - OUR EXPERIENCE WITH VALPROIC ACID

Details

Written by Lisa A. O'Brien (Machak)

Published: 20 July 2009

My daughter Mackenzie Erin - we call her M.E. for short - was born December 30, 1997. She was diagnosed with classic MSUD at 15 days, one day after being admitted to the hospital. Her metabolic doctor estimates that her leucine level at diagnosis was about 4000 µmol/l or 52.5 mg/dl. Peritoneal dialysis brought her out of her semi-comatose state. Her MSUD was under control at approximately 2 months of age, when I noticed that her eyes would flutter and roll back at times and on occasion her arms and legs would jerk randomly. We were referred to a pediatric neurologist who diagnosed a severe disorder caused by damage from the late diagnosis of MSUD.

She was started on phenobarbital and monitored with EEG's repeated every 3 to 6 months. Each one proved to be normal. Finally, after 1½ years of phenobarbital, her EEG's showed no more seizure activity, but were still abnormal. The neurologist told me that M.E.'s logic, reasoning and speech area of the brain were affected. The abnormal EEG's were just her. M.E. was weaned from the phenobarbital and went on to meet her developmental milestones pretty well with some slight delay.

M.E. remained seizure free with no medication until in February 2002. She and I were cuddling on the bed after her bath and she seemed warm. I felt her head and took her temperature. It was 102.5?. I had just laid back down with her when her eyes rolled back, and she started having a grand mal seizure. It was the most frightening thing I have ever seen other than when she almost died before being diagnosed.

She was admitted to the University of Illinois Hospital at Chicago. All her pediatric specialists are there. She was started on valproic acid because she was having seizures approximately every hour even without a fever. The neurologist dismissed the possibility of febrile seizures and her 12-hour EEG showed severe seizure activity. I need to point out that her leucine level was a beautiful 150 µmol/l (2 mg/dl) at this time.

After a week in the hospital, with valproic acid levels at a therapeutic level, we returned home. Another battle fought and won - or so I assumed.

Within 5 to 7 days, I noticed M.E.'s behavior began to deteriorate, worse than it had been. (We believe she has ADHD and will soon have a diagnosis). She became extremely irrational, acting bizarre and very aggressive. Her leucine began to climb for no apparent reason. She wasn't sick or off-diet. I made a few phone calls to her metabolic doctor and neurologist and asked, "Could this be the valproic acid causing these behaviors and the high leucine level?" (Deep down inside, a mother knows the answer to these questions and more - it's getting the doctors to listen.)

I continued to raise the question for the next three weeks while M.E. was given nothing but apples and applesauce. Her leucine continued to rise higher and higher. Her irrational behaviors became fewer and farther apart as she grew lethargic, became ataxic and started

hallucinating. M.E. is fed via G-tube, so she continued to receive her formula as usual. She had been on valproic acid for 1½ months.

She was semi-comatose when admitted with a level of 1800 µmol/l (23.6 mg/dl). Now mind you, M.E. has been hospitalized so much in her four years of life, we are a household name there. But this time was different. They did CAT scans and Mannitol was on order, but not needed. MRI's were needed but couldn't be done - too risky they said. I had gone this road with her alone since birth and had been so strong. This time I was as limp and helpless as she was while lying there.

As I searched the depths of my soul for strength, a very kind resident doctor came into the room. He said, "Mom, it says here that you believe that valproic acid is causing this metabolic crisis." I jumped up and said emphatically, "Yes, I do!" Then he stated, "But there is no data to back this up." At this point, I told him to call the neurologist and tell her I wanted the valproic acid stopped immediately!"

This very kind resident doctor then ventured on a tireless search to come up with some type of data to prove this. I had hope and strength again. Within 12 hours of our discussion, he produced an abstract describing the interaction between valproate and branched-chain amino acid metabolism. *(See a reprint of the abstract in the box below.)* The valproic acid was discontinued. Later, in a humorous moment, he and I joked about who would get the credit - I gave it to him. He gave it to me, stating that I knew all along but didn't know where to find proof to back up what I thought.

Within 24 hours of stopping the valproic acid, M.E.'s levels started to drop, and she became a little more alert. Each day in ICU there would be an agonizing wait for leucine levels of the day. Finally, after 4 days, she was discharged with a level of 250 µmol/l (3.3 mg/dl). She was now on Phenobarbital Elixir instead of the valproic acid.

Interaction Between Valproate and Branched-chain amino acid Metabolism

This abstract (summary) was given by a resident doctor to Lisa O'Brien when she became suspicious her daughter was reacting to valporic acid (valporate). Her daughter was taking this medication for seizure activity.

Abstract:
Structural similarities between valproate metabolites and metabolites formed from the beta-oxidation of branched-chain amino acids (isoleucine, leucine, and valine) suggest that valproate may utilize key enzymes of branched-chain amino acid metabolism. Genetic deficiencies in these enzymes may decrease beta-oxidation of valproate and increase formation of valproate hepatotoxic metabolites. We attempted to determine if valproate interacts with branched-chain amino acid enzymes and also evaluated the effect of valproate on the urinary excretion of the straight-chain fatty acids butyrate (C4), valerate (C5), and hexanoate (C6). We collected dosage interval urine samples from three groups of 10 valproate patients: (1) valproate monotherapy, (2) valproate with carbamazepine, and (3) valproate with phenytoin. We also collected 12-hour urine samples form 10 normal volunteers who served as controls. Valproate caused significant increase in the excretion of the deaminated acid metabolites of valine, isoleucine, and leucine. There were also significant increases in the excretion of the isoleucine metabolites 2-methylbutyrate and 2-

methyl-3-OH-butyrate in the valproate patients. Valproate caused a significant increase in the excretion of all three of the straight-chain fatty acids evaluated, and valproate appears to inhibit the four types of acyl-CoA dehydrogenases involved in branched-chain-amino acid and short- and medium-chained fatty acid metabolism.

Anderson, G.D., et al. "Interaction between valproate and branched-chain amino acid metabolism." *Neurology*, April 1, 1994; 44(4): 742-4. (Author affiliation: Department of Pharmaceutics, School of Pharmacy, University of Washington, Seattle.)
Since then, M.E.'s MSUD has remained under control, although we have run into problems with the Phenobarbital Elixir. M.E.'s behavior became very hyperactive, and she started with bizarre behaviors within a week or two of beginning the new medication. I phoned the neurologist. He said they have a lot of complaints about this medication. Apparently there is an ingredient in the Elixir that causes this (possibly a dye or alcohol). So we switched to the tablets approximately two weeks ago. I crush and dissolve them and put them through her G-tube.

I have noticed a small improvement in hyperactivity and behavior although not as much as I hoped. Much of what we are seeing could be the ADHD with the phenobarbital exaggerating the symptoms. I want to add that I was told by our neurologist that phenobarbital is usually not the anti-seizure drug of choice for children, because over time and continued use, it has been shown to lower the I.Q. by a few points.

As it stands right now, we will be doing another EEG to determine whether to continue medication or explore other choices. Our two other choices for anti-seizure drugs have severe side effects. As for M.E., she is forever smart, charming and inquisitive despite all her setbacks. She continues to amaze me each and every day. Bless her heart.

SHARING - BE AWARE OF THESE POTENTIAL PROBLEMS

Details

Written by Joyce Brubacher

Published: 20 July 2009

1. **FOOD POISONING:** It is well known that a large percentage of episodes of vomiting and diarrhea are really food poisoning and not the "flu" that is often blamed. For children and persons with MSUD, the vomiting and diarrhea that go with food poisoning can be disastrous. Be sure all foods that are to be refrigerated are not left at room temperature after a meal. Keep formula refrigerated between feedings. Keep dishes washed and use good hygiene.

You may be able to avoid flu-like episodes that send MSUD children to the hospital.

2. **ASPIRIN:** Do not give aspirin or over-the-counter medications containing aspirin to children with MSUD. Children with MSUD are very susceptible to a Reye Syndrome-like illness with the accompanying brain edema. It is very important that children with MSUD do not take aspirin or products containing aspirin. Make it a practice to read the ingredient list on all over-the-counter medications.
3. **VALPROIC ACID (valproate):** Additional research is needed to determine the safety of medication containing valproate for children with MSUD. Valproic acid has been given to some children with MSUD for seizure activity. Several parents have noted significant changes in their children when this medication was given. These reactions disappeared when the medication was withdrawn. *(See previous article and abstract.)*

Have you noticed any adverse reactions to medications in your child with MSUD? Has any adult with MSUD had reactions? The editor would be interested in hearing from you and also from professionals who could give us some insight into medications and MSUD.