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MSUD: THE IMPACT OF THE DISORDER ON THE CHILD AND THE FAMILY

Details

Written by Gabrielle Weiss, M.D.

Published: 14 July 2009

Gabrielle Weiss, M.D., Professor of Psychiatry, at McGill University spoke on this topic at our 1990 symposium in Montreal. Several parents expressed their appreciation and asked to have it printed in our newsletter. Due to its length, we did not print it in its entirety in the Newsletter. This is the complete article.

As a Child Psychiatrist, I have worked for many years as a consultant to specialized medical clinics for children with physical disabilities and chronic or terminal illnesses. In this way, I have learned over the years something about what is meant for the child to cope with being handicapped in some way, or even terminally ill; what this meant to his or her parents; how this affected the interaction between parents and child. I saw these issues as being crucial to the emotional impact of the diagnosis and the subsequent course of the disorder. However, I have worked only with three families where one child had MSUD, and am therefore not a specific expert for this condition, although I did learn some of the unique stresses, frustrations and crises which MSUD children and their families undergo. In writing for parents of children with this disorder, I want to emphasize that you, as the parents, and not I, the professional, are the experts, and while I have much to learn about the emotional impact from you, there is much expertise we can exchange which may be helpful.

Let us turn to MSUD specifically. Before the diagnosis is made, parents go through a very hard time because the pediatrician may not know at first why the newborn does not thrive. But for this disorder, the diagnosis must be made within the first 10 days or so, if the infant is to survive.

Mothers are the first to notice that something is wrong. The infant is drowsy, is not sucking and is losing weight. The pediatrician is puzzled and may change the formula. By the time the infant finally gets to hospital, he or she may be in a coma. For the parents who have been worried all along, this may be devastating. Now they do not know if their baby will live, and the parents may be warned in the Intensive Care Unit that the baby could die, or live

and be retarded. Panic results during this crisis, and it is normal for parents to hope for death on a cognitive level, but on an emotional level, to nevertheless hope with all their hearts that the baby will live. It is often a nurse who smells the sweet (maple syrupy) smell of the urine, and finally laboratory tests and dialysis are carried out and a diagnosis is made. Relief and concern follow on the parents' part. Their infant improves but the extent of the damage to the brain is not yet known, or is their ability to care for an infant with such a unique problem known to them. Their baby has a life-long disorder for which a particularly rigid diet is essential; medical care will always be required. What does all this intense period of life, death and uncertainty do to the mother-infant and father-infant bonding, which is essential for mutual attachment over the years and the cornerstone of a healthy personality?

It is one of life's miracles that most, in spite of the intensity of the upheaval, normal bonding between parents and infant takes place. It is not easy for a few, and attachment only develops when some of the fear of being unable to follow the routines required, and thus keeping the infant alive, goes away. For some of the parents, the strong bond made had much anxiety and guilt mixed in, which may later become troublesome. Too much anxiety and guilt, as well as the experience of both loving and hating their baby (who has forever changed their lives and impinged on their freedom) may benefit from professional help. These feelings are universal, but some parents succeed in dealing with them by their mutual support of one another, while others (less lucky perhaps in their own early lives) make use of professional help. When parents cannot cope and professional counseling is not available to them, or not desired by them, serious problems between the child and parents can result. These sometimes take the form of extreme over-protection, which does not allow independence and autonomy of the developing child, or there may be overt rejection, or a combination.

It is necessary and difficult to come to terms with difficult emotions: *ambivalence* (hating and loving the child at the same time); *guilt* (we, as parents, gave our child this disorder, through our genes, why did we marry?); *anger* at fate (why me?); *fear* (that as parents we cannot cope with a child with so many special demands, or fear that we do not want to cope); *sorrow* (for the child and the wish that the parents could have the disorder instead); finally a *sense of failure* (at having an imperfect child).

Somehow, most parents manage. Health professionals who label any of these feelings disturbed have never had the experience. These feeling are normal, but have to be worked through so that the child's development becomes as normal as is possible. Professional help can be very valuable.

I will now tackle a few specific questions or situations which trouble parents of children with MSUD, and which I have been specifically asked to comment upon.

Infants or children who refuse the necessary formula

Many children call the formula my milk and are revolted by the taste and smell. Even though they have had it all their lives, they find it as distasteful as we do when we smell or taste it. This is not true for all children. Some have no problems and take their milk's taste for granted. For those infants or children who refuse it, disguising the taste with a flavor may help, but not always. If the child refuses, force-feeding results and the battle is on. This

battle can go on all day long, since the formula is essential to life. It cannot ever be skipped. Some of these children have been force-fed and survived it emotionally, still loving the mother who had to do it. In time, children learn that their mothers had no choice. Occasionally a nanny, a grandmother or a friend is better than a parent in getting the child to accept the formula. I think the reason for this is that there is less anxiety in their attempts to feed.

Parents develop all sorts of unique strategies to get the child to accept the milk. They are usually successful in the end. If this is not so, play therapy can be helpful. For one child who refuses her milk, she became the mother in play. She gave her baby this poison and showed her need to be on the controlling side of the equation. She later set the rules for how she would take the milk she needed: how thin, how thick, how much, how often, how flavored.

What to tell your child

Every parent will get the advice to tell the truth, but it is more complicated than that. The truth has to be told in ways that are meaningful to the child's developmental stage. Amino acids, enzymes and genetics will mean something to the adolescent. The 2 year old only has to know he or she is fine as long as he drinks and eats only some things. If the child does not comply, hospitalization and illness will result. That not eating can be fatal, cannot be understood until the child has a concept of the permanence of death, which occurs between 5-7 years of age. Hence, parents have to become skilled at telling the child what he needs to know when he needs to know it, and in language that is understandable. The child has to learn that he or she can never eat some things that smell so delicious. One child whould have done anything to have scrambled eggs just once for breakfast. Children eventually adjust, but not without some anger and sadness, and a knowledge of being different from others.

Learning disabilities

These are frequently associated with MSUD. They may be the result of late diagnosis or intermittent poor control of blood levels, sometimes as the result of intermittent infections. Learning disabilities may require special remedial help and, for some, are associated with hyperactivity and poor ability to inhibit impulses. Even when present, the child eventually is likely to become self-sufficient as an adult, with or without completing college or even high school. Self-sufficiency in adulthood may depend on the child's emotional stability and independence as much as on the degree of learning disability.

The parents go through very upsetting periods every time their child has to have psychological testing. They understand the day-to-day variability of the child's cognitive functioning depending on blood levels, which, at times, the school psychologist may not understand. A single bad test result, be it on reading level or overall intellectual ability, may not be reliable. Parents of MSUD children have to educate professionals on this. Their attempts to do this may be misinterpreted by the professional as denial or over-protection. It should be the physician's task to interpret this variability of cognitive functioning to school authorities.

The thin line between protecting a child and over-protection, leading to dependency
For parents who have a child with MSUD, this thin line is not easy to find. While every situation is different, and a mental health professional who knows the family well can be helpful, since he or she is able to take a more objective stand, a few guidelines may be helpful. It is normal to feel sad for your child because of the life-long restrictions of diet and uncertainty about outcome in the future that the child will have to handle maturely. But it is a mistake to pity your child excessively; some other illnesses are much worse. If a parent has too much pity for the child, the child will learn to pity himself or herself. Nor can a parent make it up to the child by giving material things or letting the child get away with things. Upbringing has to be the same as for a child without the disorder, except for the dietary restrictions and accommodation to cognitive (learning) difficulties when present.

Slowly, the child with MSUD has to take responsibility for his or her own diet and this makes it possible for the child to go to camp, sleep over at friends' houses, and to visit relatives. It is an essential part of child development to learn to leave home. The child who is excessively over-protected and babied does not develop the necessary sense of self to leave his parents. Because of the close bond between mother and child, resulting from early necessary protection, some mothers require professional help to learn to let their children grow up. Fathers can help a great deal since they are usually not as closely tied to their children. By becoming closer to their wives, fathers can enable them to allow ever increasing independence in the children.

Family interactions
What effect does the child with MSUD have on the parents and on the larger family, including grandparents? Where medical costs are not covered (as they are in Canada), a financial burden may be experienced. There will also be an emotional burden on the father to give out strength and stability to his wife and all the children. Some fathers do a magnificent job of shouldering these extra responsibilities. In some families, the father is more the breadwinner and not closely involved with the mother and child. Occasionally, he has not chosen this role but has felt pushed out and unwanted in the close mother-child bond. When this happens, it spells trouble later, because father is needed to facilitate the mother's allowing the child to grow up, even with the problems of MSUD. In this situation, counseling is often aimed at strengthening the marital bond, thus creating more space in the mother-child bond.

The brothers and sisters of a child with MSUD may actually feel envy rather than pity. They may rebel in order to try to get more attention. One brother told me that when he was 8 years old, he wished he had MSUD. Special effort had to be made under the given circumstances to provide sufficient attention to the normal children in the family.

Grandparents, uncles, aunts and cousins (the large family) can, if available, be very helpful. Cousins who are a similar age can add to the necessity of socializing with children so that isolation does not take place. (Of course, the child's friends from the neighborhood or school play a similar role.) Grandparents and other relatives can help bring about independence for the child with MSUD, by enlarging the number of important people and providing places to stay away from home. Grandparents have to be careful not to be too worried or to spoil their grandchild. They can be very helpful to their children -- the parents -- when they are supportive and not critical, and raise their children's self-esteem as parents.

Health Professionals
We have a particularly fortunate situation in Montreal. The health professionals who care for the children with MSUD and their families truly join the families, and in some ways become family members. Yet, at the same time, they can keep sufficient professional objectivity, enabling them to give sound medical and psychological help. Ideally, medical care-givers need to tread this balance of being part of the family, with no professional condescension, but rather with respect for the many unavoidable hurdles. Yet, they need to keep sufficient distance to accurately appraise why and when the family can and needs to use their help. When psychologists or psychiatrists are part of the team, much benefit results.

Families who do not have good access to comprehensive medical or psychological care have to become assertive advocates for their children until the required services are found, a role requiring a degree of assertion for which parents may be ill-equipped. Parent organizations, like this one, and self-help groups can be very valuable. Parent groups have to avoid two patterns that are not always easy to avoid. One is that parents can become competitive with one another as to whose child is doing best. Another hurdle is that when an unfortunate thing happens to one child in a particular family, it becomes a new threat to all and could lead to more general pessimism. Sharing all the possible worst things that could happen, but probably will not, is not helpful. In spite of these and other difficulties, parent organizations are enormously effective and influence health professionals to understand the disorder, not only in terms of the biological defect, but in terms of the psychosocial aspects of the child's development. Parent organizations provide the impetus for parents to mobilize better services at all levels for their children. In getting together to do this, they feel empowered and valuable. Parents are our teachers, just as we share with parents our specific medical and psychological expertise. Parent organizations and meetings facilitate this interaction.

GENETIC CAUSE OF CLASSIC MSUD IN THE MENNONITE POPULATION DISCOVERED

Details

Written by Alice T. Mazur, Sheila Noone, Randall A. Heidenreich, CHOP

Published: 14 July 2009
The year 1990 was a pivotal year for the diagnosis and care of patients with maple syrup urine disease. The mutation (changed gene) responsible for classic MSUD in the Mennonite

population was discovered. This exciting event was initially reported by Dr. Matsudu of Kumamoto, Japan, confirmed by Drs. Matsudu, Heidenreich, Sefal et.al. of Japan, and Philadelphia, PA and Drs. Fisher, Fisher, Chuang and Cox of Dallas, TX. The mutation is a thymidine (T) to adenine (A) change in El alpha subunit of the gene. This change results in complete loss of activity of the Branched-chain ketoacid dehydrogenase enzyme leading to symptoms of MSUD. As outlined in the following paragraphs this information will directly impact individuals of Mennonite faith and other individuals discovered to have the same mutation.

The gene is the fundamental biological unit of heredity. Genes are transmitted in pairs to individuals from their parents, one from father and one from mother. Genes are located on chromosomes which are in turn located in the nucleus of the cells of the body. Inside the nucleus of each of the body's trillions of cells are located 23 pairs of chromosomes. Coiled inside each chromosome is the body's genetic material, DNA, or deoxyribonucleic acid, the blueprint for human life. Arranged along the chromosomes are the genes, which are the fundamental units of heredity.

Genes instruct the body's cells to make proteins and determine everything from eye color to susceptibility to genetic diseases. Each rung of the DNA twisted rope ladder contains a pair of four chemical units known as nucleotides. Adinine (A) always attaches to thymine (T) and cytosine (C) always pairs with quanine (G). The characteristic properties and fundamental activity of proteins, such as enzymes, depends on the sequence of the nucleotides. Genes act as indirect patterns for reproduction of body proteins, which are made of chains of amino acids.

Classic MSUD in the Mennonite population is due to a mutation of the sequence pattern of the nucleotides. Individuals with MSUD, or homozygotes, have inherited a gene with the mutation from both mother and father. Those individuals who have inherited one gene with the mutation from either parent, but who also inherited a normal gene from their other parent are called carriers or are heterzygotes of the disease.

It is not yet known whether non-Mennonite individuals with classic MSUD also have the same genetic mutation. One individual with a variant form of MSUD who was tested, did not have the same genetic mutation. There may be more than one genetic mutation responsible for classic and the different variant forms of MSUD. Work is in progress both at the Children's Hospital of Philadelphia as well as other centers to answer these questions.

Our studies have shown that the longer the diagnosis is delayed, the more likely it is that there will be some damage to the brain. Early treatment is critical in these children for the best outcome. Newborn screening will help to identify the children, but the results of testing will probably not be available for several days and usually, the children will already have the symptoms. The usual symptoms are vomiting, poor feeding, floppiness sometimes alternating with tightness of the limbs, arching of the back and neck, excessive sleepiness, seizures, and the characteristic odor of burnt sugar or maple syrup. It has been estimated that classic MSUD occurs in 1 in every 176 live births in the Mennonite population. The identification of the MSUD mutation in the Mennonite population will help to identify carrier status. Once two parent carriers have been detected, they can seek early diagnosis and treatment for potentially affected infants. Infants have biochemical abnormalities on the first day of life, long before symptoms occur, so diagnosis should be made quickly and treatment

started before serious complications occur.

Who should be tested?

- All individuals who have family members with MSUD should be tested for the gene mutation.
- People marrying a known carrier.

What does the test involve?

The test is simple. Specimens can be obtained at home and mailed. It involves pricking a finger with a special sterile lancet, blotting several drops of blood onto a special sterile filter paper and then mailing the paper to our office.

(NOTE: See under Genetics in the Index for up to date information on this type of testing.)

OUR SPECIAL STORY ABOUT LEANNA

Details

Written by Mary Ann Peters

Published: 14 July 2009

On April 3, 1985 at 3:58 a.m., I gave birth to a beautiful baby girl which we named Leanna Marie Peters. My husband and I were so excited because we had a son, and she just completed our family. We were discharged after three days in the hospital. During the hospital stay, I remember one of the nurses commenting on Leannna's sucking action. She thought it would be better if I nursed her since she was not sucking very good with the bottle. I nursed her that night, and she seemed to do well. She did well for a few days until I noticed her sleep patterns to be a bit restless. She would frequently cry in her sleep and make some very strange noises. I then noticed she wanted to sleep more than to nurse, and it became an effort to get her to suck.

A week after we were discharged, I received a phone call from the office of the pediatrician who examined her in the hospital at the time of birth. He was calling to let me know that one of her test results from the newborn screening was a bit of concern to them, and asked that I bring her in.

After examining her in his office that afternoon, he instructed us to go directly to Massachusetts General Hospital to be seen by Dr. Vivian Shih. At that point in time, we were still not sure how serious the situation was becoming. We went to Massachusetts General Hospital, and she was examined by Dr. Shih who verified the diagnosis as maple syrup urine disease. She also informed us that our daughter was dehydrated. Dr. Shih gave us a brief description of her disease and tried to answer all our questions.

My first question to her was, Can't you operate? Unfortunately, as we all know, an operation

does not work, just a constant diet of protein free foods. At that point, we finally realized how serious her condition was and started asking the questions, Why us, why her? But after much soul searching we realized we could handle it and life would go on much as before.

She remained in the hospital for two weeks and required peritoneal dialysis. Her progress was slow at first, and I become a bit nervous every time she spit up or fussed. We managed to get through those two difficult weeks, and she has now turned into a very outgoing and personable little girl.

We did encounter a setback that caught us off guard when she was three years old because everything was running smoothly. But as we all know, those are the problems these children face every day of their lives. The setback was a stomach virus that caught her on Christmas Eve. She was hospitalized the day after Christmas. She remained in the hospital for two days and was then sent home for constant monitoring. Now I try to take one day at a time and try to make her life as normal as possible.

She attends YWCA kindergarten and really enjoys interacting with other children. Her teacher has encountered some learning difficulties that we are trying to deal with at the moment. With the advice of her specialist, she is now seeing a psychologist at Massachusetts General Hospital who plans to administer a test at age six to determine what her learning disabilities are and how to handle them. We are hoping for the best, and realize the school years may require a constant effort for Leanna to keep up with her classmates.

An excerpt from Mary Ann's letter to the editor
I just had a scary incident when Leanna was sick. She had some type of stomach bug and threw up once or twice. But it caught me off guard when she saw worms and snakes in her room. There was nothing there. Talking to her specialist, I found that when MSUD children have high leucine levels, they may hallucinate. Other parents may be interested in this information, especially if they haven't experienced it yet.

FAMILY HISTORY - CORY ECK

Details

Written by Renee Eck

Published: 14 July 2009

This family history is about Jim and Renee Eck and their son, Cory, who has classic MSUD. I think Mrs. Eck expressed so well the underlying stress experienced by many families. Even when things are going well, there is always the next episode right around the corner. I admire so many of the couples I have had contact with for their courage in not being afraid to deal with these stresses. This reminds me so much of my son Mike's diagnosis. No one said it was easy.

Jim and I were married in 1977. After five hard years of learning about each other, we decided to have children. In 1983, we had a healthy daughter named Crystal. After a year or so we decided to have another child. Cory was born January 14, 1985, three days after our daughter's second birthday.

Everything seemed normal until about the fifth day. Cory never seemed to cry because he was hungry. And most of the noises that he made seemed more like fidgeting or very weak moans. On that fifth day, we were being discharged from the hospital when I asked the doctor about him not eating well and acting as if he were uncomfortable most of the time. I was told not to be an over-excited mother. (This was not my regular doctor.)

On the first evening home Cory had a seizure. I really wasn't worried about it, because I have known of others to have seizures that were not harmful. But I did not forget it. On the eighth day, Cory seemed a little better, but I took him to see our regular doctor. Her conclusion was that Cory had a feeding disorder, and I was shown how to force feed him. I did this all through the night not getting more than four ounces of formula in during that 10 hour period.

On the ninth day I took him to Children's Hospital in Columbus, Ohio. The doctor came to the same conclusion as our regular pediatrician, that Cory had a feeding disorder. We were sent back home doing the same thing as the day before.

On the tenth day, at around 5:00 a.m. in the morning, Cory had the second seizure that I noticed. I let him sleep until 9:00 a.m. and then tried many ways to get him awake. I put cold water on his feet and face; I bounced him around. I did everything I could think of, and it did not work. I then took him to the same doctor that saw him on the eighth day. She was surprised at the difference in him. She called Children's Hospital in Columbus, and he was admitted in a semicoma. Cory was put on IV's until they learned what was wrong.

On day twelve we were told Cory had classic MSUD. At first I was still very optimistic. I remember thinking, we'll fix him up and send him home. I soon learned it wasn't going to be that easy.

On the fifteenth day Cory wasn't responding as well as they hoped, so they put him on dialysis for three days. It did not work for Cory, so the only other thing to do was to use IV's and wait.

Cory was admitted to Children's Hospital on Jan. 22, 1985 and released March 22, 1985 to a very unsure mother. Since that very rough start we have unfortunately had a lot more rough times. Cory was in the hospital five times the first year. From ages 2 to 3 he was a lot more stable, hospitalized only two times.

At age four he had a lot of ear infections and a lot of vomiting illnesses. He was also operated on for tight ham strings in his legs. They were released so he would hopefully be able to walk and stand. It did help, but he still had to have a lot of therapy. He was hospitalized nine times that year. At age five he is back to ear infections and vomiting and has been in the hospital eight times.

Cory turned 6 years old on Jan. 14, 1991. On Jan. 8th he started the new year in the hospital by having tubes put in his ears for the third time. We are hoping that just because he starts the year out in the hospital, that he won't make it such a regular habit like in his past. For some strange reason he likes it there. He likes the attention he gets from all the nurses that all know him very well. I think he thinks he has about twenty mothers, and he can't choose which one he wants to keep.

I am grateful that this support group exists because I have called a lot of people on the parents' list for advice at different times. I would like to thank everyone for all the help they have given me. Even if you feel like you didn't help me, just having someone I could talk to that understood was a big help.

RESPONSES TO THE NEW CLINIC AND THE USE OF DNPH

Details

Written by Various Authors

Published: 14 July 2009

Enos Hoover, the father of Edith Hoover, a 16 year old with MSUD, has been instrumental in starting the Clinic for Special Children. As a member of the board of directors, he represents families with MSUD children. Following is Enos and his wife, Anna Mae's recent experience with the Clinic's services.

We have found the services of the Clinic a big help in keeping Edith's condition under control. We started using the 2,4-DNPH test regularly, and learned that her leucine was often slightly elevated (5 to 10 mg/ml). Also ph was low (5 to 7). So we started using sodium bicarbonate (20 gr/day) which keeps the urine ph at 7 to 9, and keeps the DNPH clear more often. We also cut back on formula to 14 oz./day and give 24 cal./oz. when levels are low.

When we have a blood test done at the Clinic we get results in 1 1/2 hrs. at a fraction of the previous cost. Our new grandson's negative diagnosis was made at 26 hrs. after birth! Most of the midwives in Lancaster County are now using the DNPH on all their newborns. So I believe we made progress with MSUD in the past year.

The new building is ready at this time. Much of the labor and some materials were donated. I know we would have used a local care center such as this earlier, but I suppose the time was not right yet. It is really an answer to our prayers, and we are sure it will also be a help to many younger parents and special children.

Anne Fredericks began taking her son to the Clinic and I asked her for her comments. This is from her letter.
As to your question about Dr. Morton, I feel that he has been an answer to our prayers. He is such a knowledgeable man but also a very caring man, and Jeff really likes him. We have had many problems, and he has been so supportive. We now use DNPH and check ph as well as ketones. I just feel I have some better ways to keep on top of his levels. He takes so much time to explain things to us and to Jeff. We're all so thankful that Dr. Morton has moved to Lancaster.

Peter Shaffer and his wife Sharon from Kentucky have used DNPH for 9 years. Peter explains how they use it.
Ever since Jessica was diagnosed 9 years ago we have used DNPH testing. DNPH is a chemical reagent that is mixed with urine. When it is negative it is a clear yellow. When it is positive, it becomes a cloudy yellow. The more positive the more cloudy. We rate our readings negative or 1, 2, 3 or 4. When we reach the 4 level the DNPH test looks almost like mustard. It is so thick you cannot see through it.

We use the DNPH as an indicator of how Jessica is doing. We do not use it alone. We also utilize keto-sticks. However, when we hit a 4 DNPH, we are also hitting the highest reading on the keto-stick.

We also pay close attention to neurological symptoms such as the loss of balance, slurred speech, drowsiness. In Jessica's case we have seen high DNPH's with no neurological symptoms (very rare) and even occasionally severe neurological symptoms, but low DNPH. Like most children, just when you have them figured out, they change.

I would like to share my experiences. (The Editor)
At the symposium in Montreal last year we learned that Dr. Charles Scriver's patients used DNPH for years. Concerning his use of the test for home monitoring he wrote, There are many ways of looking after a patient with MSUD. This is just one of them. I say this because two other major centers don't subscribe to the monitoring of the keto acid, (and there may be no difference in outcome). I think the use of the test in the home gives the parent some sense of control.

Dr. Scriver's last statement pinpoints the major advantage of DNPH as a tool in home monitoring. I have found it so helpful in my 26 years of caring for children with MSUD. Frequent blood tests were not feasible as we lived 160 miles from our medical center.

Correlating blood tests with DNPH reactions in two children over a period of time helped me learn to judge their amino acid levels quite accurately. This took much of the guess work out of daily monitoring. I could implement diet changes at the first sign of elevated levels and our children seldom needed to be hospitalized for illnesses. It also aided me in varying their diet.

I was given keto-sticks to use twice that I can remember when our children were sick in the hospital. I was disgusted because they were obviously sick, but the keto-sticks showed no reaction. Later I did get some to try at home but never saw a positive reaction. They were totally

useless for us. In contrast to Peter's report, we have seen a very positive reaction with DNPH frequently without neurological symptoms, usually caused by stress or from an extra gram of protein eaten that day. The test changes rapidly, sometimes in an hour on those occasions. Evidently there is a difference in how some children respond to the different tests.

For many years I used two test tubes each time I tested urine. I would put 20 drops of urine in each and then add the reagent to only one of them. If the urine was cloudy to start with, I could watch both to see if the reagent was causing it to become more cloudy. I never had a problem with this method as taught to me by our doctor, Dr. Allen. I will always appreciate him introducing me to DNPH.

Shayla is 21 yrs. old and has been responsible for monitoring her diet for several years. I would be very uncomfortable allowing her this independence if she did not use DNPH. She cannot tell if her leucine levels are elevated by how she feels physically and has shown no distinct neurological signs with high levels for years.

Our friends, Leon and Dianne Kennedy have recently taken their second foster child with MSUD into their hearts and home. I asked her how she feels about using DNPH. Without a moment's hesitation she answered emphatically, I wouldn't even consider taking an MSUD child without DNPH! For some of us, it is a necessity.

A word of caution on DNPH
DNPH is an acid and must be handled with care and kept out of reach of children. I've been told one can get an acid burn from it. Though we've never experienced that problem in over 23 years of use, I do advise caution. Do clean up any spills immediately, as it stains easily. It should be kept in a dark bottle out of bright light, as light tends to weaken the solution.

DNPH is not a miracle worker but a very helpful aid in caring for persons with MSUD. It would be great if all parents would have the opportunity to try it if they are interested. My thanks to Dr. Morton for his efforts in investigating 2,4- DNPH as a tool in home monitoring.

LETTER FROM DR. MORTON

Details

Written by Joyce Brubacher

Published: 08 July 2009
April 12, 1991

Dear Joyce:

Last summer Tom Lundquist, a senior medical student at Johns Hopkins Medical School, and I studied the use of the urine DNPH test to monitor day to day control of MSUD. We had the help of Enos & Edith Hoover and several other Lancaster County families who have children with MSUD. I long ago promised to summarize our findings for your newsletter and regret that my busy work schedule has prevented me from writing this letter before now.

Our reason for evaluating the use of DNPH will be obvious to parents of children with MSUD. Because of the sensitivity of the disorder to minor infections and small changes in diet, measurement of plasma amino acid levels at monthly or quarterly intervals as practiced in most centers providing specialty care, has limited value for the day to day management of the disorder by families and local health care providers. Parents have long recognized the need for a test which would allow the disorder to be monitored daily at home in the same way that diabetics monitor blood glucose levels. Several families have used the urinary DNPH keto acid precipitation test to assess metabolic control and have found the test to be practical for in-home use and helpful in the management of their children with MSUD. We were asked by the MSUD Family Support Group to conduct formal studies of the urine DNPH test, to verify its accuracy, and to comment upon the value of the test for routine care.

Comments About The DNPH Method Use In Our Study:
Our purpose was to study the relationship between the DNPH reaction in urine and the levels of keto acids and amino acids in blood. We obtained twenty paired blood and urine samples from children who have MSUD and used a Hewlett Packard gas chromatograph-mass spectrometer and an amino acid analyzer to measure the branched chain keto acids and amino acids concentrations in the samples. We monitored DNPH test each day for 100 days in a 16 year old girl to gain insight into the day to day changes in her metabolic control. We also tested urine samples from 100 newborns to see if the test was often positive in that age group.

The DNPH method we used is the same as you have used and is described in Dr. Vivian Shih's book Laboratory Techniques for the Detection of Hereditary Metabolic Disorders. The DNPH reagent was purchased from Eastman Kodak Company and 100 mg of DNPH was dissolved in 100 ml of 2N hydrochloric acid. An equal amount (1 cc) of urine and the DNPH solution (1 cc) are mixed in a clear test tube then after 10 minutes the cloudiness of the mixture is noted. Although simply noting whether the mixture is clear or cloudy provides the most information, we found it useful and easy to score the cloudiness on a scale of 0+ to 3+÷0+ (clear), 1+ (very slight cloudiness), 2+ (cloudy but possible to read print through), or 3+ (too cloudy to read print through).

The manner in which the DNPH test is done is important, especially when the 0+ to 3+ scale is used. The urine and the DNPH solution must be clear before being mixed. If the urine sample is cloudy, it should be allowed to sit for 15 to 30 minutes to see if it will clear (or it could be centrifuged). The DNPH solution often has a small amount of precipitate at the bottom of the bottle. Avoid adding this precipitate to the urine sample. A clear, clean test tube of a standard size should be used or it may be difficult to use the scale of cloudiness from one test to the next. The test tube we used was an inexpensive clear plastic tube that

measures 1/2 inch across and is 3 inches high (12x75 mm). It is especially important to use equal amounts of urine and DNPH. The sensitivity of the test and the 0+ to 3+ scale depend upon a 1 to 1 mixture of urine and DNPH.

Dr. Berry and others at Children's in Philadelphia were initially concerned that the DNPH test was insensitive. After some discussion it was found that the DNPH method used by Children's called for only 4 to 5 drops of urine in 3/4 to 1 cc of DNPH solution. Using the Children's method a positive result would be obtained only when very large concentrations of keto acids were present in the urine because such a small amount of urine was used for the test.

Observations:
The values 1+ and 2+ correlated with blood leucine levels from 5 to 10 mg/dl while a strong 3+ reaction always indicated increased blood levels of the keto acids and almost always predicted that the leucine concentration in blood was greater than 10 mg/dl (> 760 µM). We also found that during illnesses, concentrations of branch chain keto acids increase in the urine in parallel with the rise of branched chain amino acids and keto acids in the blood. The DNPH reaction becomes positive long before ketones appear in the urine. Therefore it is a much more sensitive indicator of poor control than keto-sticks or Acetest tablets. The DNPH reaction is also much more sensitive than the MSUD odor as a predictor of illness.

We found, as you had reported, that excretion of keto acids increase 12 to 24 hours prior to the onset of fever, diarrhea, and other clinical signs of infection. We also observed that the DNPH test is often positive even when children with MSUD seem well. During an initial observation period with one girl, the DNPH test was 2 or 3+ on 27 of 50 days and was often positive for several days in a row. However, with simple changes in therapy, the test was positive only 10 of 50 days and cleared rapidly with minor adjustments in the intake of protein, MSUD formula, and bicarbonate.

The test is surprisingly specific for the keto acids of leucine and isoleucine. DNPH precipitation does not occur with other keto acids in the urine to any significant extent. Even urines that are strongly reactive with Acetest because of diabetic ketoacidosis do not give false positive DNPH tests. We tested 100 urine samples from newborns and found only 1 weak false positive.

There are a few circumstances when the DNPH result can be misleading. After a meal, the amino acid levels in blood rise rapidly as protein is digested and absorbed and then fall as the amino acids are taken up into organs for use to make protein. The rise in leucine after a meal is not always accompanied by a rise in the keto acids in blood and urine. The rate of conversion of the amino acid to the keto acid and the time of excretion into the urine depends upon several factors including the amount of fat and calories and protein in the food, and whether the person is metabolically well or ill or dehydrated. The test is most reliable when the first morning urine is tested or with a sample obtained at least 4 hours after a meal.

Another important circumstance that can produce a misleading result is the rapid fall of isoleucine and the keto acids that occurs during the recovery period of an illness. When a patient is on MSUD formula alone and the branched chain levels are falling, the keto acids

fall more rapidly than the amino acids. Also, isoleucine, which usually contributes about 30 to 50% of the DNPH precipitation, falls more rapidly than leucine. For these two reasons, the DNPH test may become almost clear when the leucine level is still above 10 mg/dl. This is a time when a blood amino acid measurement is useful to guide the re-introduction of protein and determine when isoleucine & valine supplements are needed.

It was our opinion that clinical illness was more closely related to changes in blood keto acid levels than the amino acid levels. Apparently Dr. Scriver in Canada and Dr. Berry at Children's have also observed this. With more research we may find that the management of episodic illnesses should be focused upon blood levels of keto acids rather than amino acids. The DNPH test may, with further study, prove to be a very good indicator of metabolic illness and provide additional insight into the biochemical basis of episodic illnesses.

Joyce, you will appreciate that much of what we learned simply confirms what you and a few other parents of MSUD children have known for some time - the urine DNPH test is a simple, inexpensive way to monitor the day to day treatment of children with maple syrup urine disease. Routine use of the test can provide parents and children with incentive for better dietary management. More important, the DNPH test can detect the rise of branched chain keto and amino acid levels in blood that often accompany common childhood illnesses and allow parents or local health care providers to make changes in therapy which will usually prevent severe metabolic illness. Finally, our preliminary studies indicate that in the newborn with MSUD, the DNPH test should become positive between 48 to 72 hours of age and we expect there to be a low false positive rate. The urine DNPH test should allow families or local health care providers to readily recognize MSUD in the newborn before the infant becomes severely ill or damaged.

At the Clinic for Special Children, we will continue to learn from such studies and gain new insight into the biochemistry of MSUD and other biochemical disorders. Although we all hope that genetic research will ultimately lead to new treatments for MSUD, we should recognize that none of the children who now have MSUD will soon undergo gene replacement and be cured of their illness. Gene replacement will be of little benefit to those children who have severe brain damage because of delayed diagnosis or poor biochemical management. Prevention of permanent damage to the brain, the quality of the lives of these children, and in fact, their very survival, depends upon an understanding of the biochemical basis of the disorder and upon efforts to offer care that is effective, practical, and accessible to those who need it.

- Sincerely, Holmes Morton, M.D.

DR. MORTON'S CALLING

Details

Written by Joyce Brubacher

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Clinic Visit

The first week in January 1991, Wayne, Shayla & I stopped at the Clinic for Special Children in Lancaster County, PA. We met Dr. Holmes Morton, the founder, at the home of an MSUD family the winter before. Now we were visiting his unique Clinic in this temporary location.

Dr. Morton had just returned from visiting a family. His slightly rumpled look attested to his sixteen to twenty-hour workdays. His devotion to his work and the families of his patients is undeniable.

Stepping into the lab, we were surrounded by high-tech equipment. Dr. Morton seemed in his element as he moved about the room explaining his research to improve diagnosis and care for children with inherited metabolic disorders.

We asked if he would run a test on Shayla's blood. No problem - he could run it while we were talking. In one hour, while we watched, he completed the test with a print-out of her current amino acid levels. He saved some blood to check keto acid levels later. A urine 2,4-DNPH test showed a negative reaction. How efficient!

Amish & Glutaric Aciduria

A Harvard Medical School graduate and pediatrician, Dr. Morton developed an interest in this area of the country during a research fellowship in metabolism at Children's Hospital in Philadelphia. In June 1988, he diagnosed Glutaric aciduria in a Amish boy who was previously identified as having cerebral palsy. There were only eight cases of this disorder documented in medical literature at that time.

With the help of local midwives, Dr. Morton began gathering urine samples of Amish newborn infants to test for Glutaric aciduria. He went from farm to farm to check on children diagnosed or suspected as having the disorder.

During this time he gained the trust of the community and made an important friend, Rebecca Huyard. She is Old Order Amish and had fifteen years teaching experience in Amish schools. Five of her sister's seven children had become mysteriously ill. Two had died and the others were physically disabled. Dr. Morton diagnosed their problem as Glutaric aciduria. Now Rebecca helps teach preventive care at Amish social gatherings and is Dr. Morton's office manager.

Children with Glutaric aciduria are normal at birth and usually healthy for the first few months of life. Under the stress of common childhood illnesses, such as diarrhea or infection, Glutaric acid builds up to toxic levels and causes life-threatening metabolic illness and brain damage. Untreated or undiagnosed infants may lapse into a coma and die within a few hours after becoming ill with diarrhea or an ear infection. Children who survive are often left with paralysis and uncontrolled movements which is commonly referred to as

cerebral palsy.

Through his research and clinical work, Dr. Morton believes the disorder is treatable and the severe effects can be prevented. His strategy for treating children with Glutaric aciduria is similar to that of caring for children with MSUD. **Recognizing the condition before brain damage occurs is crucial!** This is the reason the Clinic established a voluntary newborn testing program.

Long term care involves restricting protein, preventing acidosis and careful monitoring of blood Glutaric acid levels during infectious illnesses. If hospitalization is needed, Dr. Morton admits the children to Lancaster General Hospital directly under his care. The administration and medical staff of the hospital are very supportive. Therapy has prevented progression of brain damage.

Since diagnosing the first case of Glutaric aciduria in Lancaster County, Dr. Morton has diagnosed 19 cases. Five infants were found in the past year through the Clinic's newborn testing program. He estimates that 1 in 200 Amish infants in Lancaster County will inherit the potentially deadly metabolic disorder. But Dr. Morton is there when needed, even at the door!

Mennonites & MSUD

We who are familiar with MSUD will notice many similarities in these two disorders. While at the Children's Hospital, Dr. Morton cared for children with MSUD. Many of these children were from Mennonite families in the Lancaster area. There was an apparent need for a more accessible and consistent source of medical care.

The Amish and some Mennonites do not have automobiles or health insurance. When these children become ill, careful monitoring is necessary throughout the illness. Traveling to Philadelphia and hospitalizing the sick child is stressful to the child and family as well as costly. A Clinic proposal appealed to the Lancaster area Amish and Mennonite families. Since the churches of the plain people help pay family medical bills, the families solicited help from their churches.

A Vision Becomes Reality

Dr. Morton envisioned a clinic to provide diagnostic services and medical care in the community at affordable prices. In April 1989, he and his wife, Caroline incorporated a non-profit organization called Clinic for Special Children. Frustrated in their efforts to get financial support, they applied for a second mortgage on their home. Then an article about this country doctor was published on the front page of the Wall Street Journal on Sept. 20, 1989. More than 500 people from 43 states responded with contributions for the Clinic and the dreams and needs of many began to become reality.

The Hewlett-Packard Co. donated the gas chromatograph/mass-spectrometer needed in testing for Glutaric aciduria. The Lancaster General Hospital donated temporary office and lab space. The amino acid analyzer used for testing and monitoring MSUD was purchased through donations from local Mennonite churches and an anonymous donor.

These donations enabled the Clinic to cut costs significantly. The test for Glutaric aciduria at the Clinic costs $35 compared to approximately $300 at major medical centers. Diagnostic tests for MSUD at major medical centers run $200 to $400. A blood sample of a newborn can be delivered to Dr. Morton an hour or two after birth. An hour later, the test is completed at a cost of $45.

Two new cases of MSUD have been diagnosed at the Clinic, one at 12 hours and the other at 20 hours of age. Since the infants were well and had low levels, therapy was started without hospitalization. Two older children with MSUD were treated for dehydration at Lancaster General, put on IV's, closely monitored, and recovered quickly.

Clinic Raising

After Dr. Morton detected Glutaric aciduria in a new born Amish girl, saving her health, the grateful Grandparents made available a beautiful site for the new Clinic. We visited the building under construction during January of this year. The traditional timber frame building sits on sloping pasture land nearly surrounded by trees. The long curving driveway leads off a small country road. It all bespeaks quiet, peaceful country life - just perfect for these people who avoid worldly, modern ways.

Here is an account of the Clinic raising day. I summarized an article from the *Nov. 19, 1990 Wall Street Journal*, adding remarks of my own.

The Clinic was raised in the traditional way, like the area barn raisings. One morning last Nov., over 50 men, most of them Amish and Mennonite farmers, arrived at the site near Strasburg. They pounded stout oak pegs into holes at the joints of hefty wooden posts and beams. The men raised these massive timbers by standing shoulder to shoulder in long lines of twenty or more men as volunteers steadied the beams with heavy ropes. One hundred six people attended the raising, offering help and moral support.

By noon, the first floor was framed and the workers headed for the nearby farmhouse and lunch. They washed in buckets of soapy water on the front porch, and then bowed their heads in a silent prayer of thanks to the Almighty God who made this day possible. The big kitchen held more than one hundred people at a time. This is where the Amish women prepared the food for the hungry workers and their families and where folks sat eight or nine to a bench eating soup from bowls held on their laps.

After lunch, twenty carpenters straddled joists above the ceiling frame of the first floor and pounded the next beams in place. No one barked commands; this was real teamwork - skills taught from generation to generation.

In the middle of the afternoon the rafters started going up. Soon the finished roof frame completed the silhouette. By four o'clock it was time for farmers to head home to do the evening chores. The dream was coming true.

Ready for Use

The Clinic is nearly completed at the time of this writing and plans are to move into it in April. Dr. Morton says, "I know I'll spend the rest of my life working in this building. I believe

we can prevent brain injury in the majority of the children who have Glutaric aciduria. I expect that over the next ten years the fate of 50 or more children will be determined by the success or failure of the Clinic. That provokes a frightful sense of responsibility in me. That's what motivates my work."

I wrote this article using information from various sources including newspaper articles, a Clinic newsletter, personal contacts, and information supplied by Dr. Morton.

- **Joyce Brubacher**

Editors note:
The terms Amish and Mennonite may be synonymous to many of you. I feel it is important to clarify the difference for medical reasons. Although these two groups originate from the same areas of Europe, particularly the Swiss Palatinate, the groups separated in 1693 and have been separate identities for almost 300 years. Amish still wear the distinctive plain attire but not all Mennonites continue practicing this sign of separation from the world. Genetically there has been little mixing until the past 30 to 50 years. Couples always marrying within their own religious denomination result in extensive intermarriage. Thus, inherited diseases common in one group may be virtually unknown in the other - such as the MSUD in the Mennonites and Glutaric aciduria in the Amish. However this may be changing as today numbers of Amish are joining the Mennonites.