

POSITIVE EFFECTS OF HYPERBARIC OXYGENATION IN CERTAIN MITROCHONDRIAL CYTOPATHIES

“All life takes place on a cellular level. This is the first scientific proposal that hyperbaric oxygenation may selectively turn mitochondrial genes on and off.”

- Richard A. Neubauer, M. D. -

INTRODUCTION

The simplest life on earth, as we know it, occurs in cells. Over the millennia, as cells evolved into more complex organisms, the new life depended upon the integrated and coordinated activities of thousands, millions and even billions of cells, each one requiring appropriate oxygen and glucose for respiration, metabolism, production of energy, adaptation, reproduction and overall survival.

For cells to carry out their unique functions they require a variety of foods with which to build their various cellular structures as well as their unique proteins, lipids and carbohydrates and from which the cells extract the energy to carry on all their vital activities.

The energy is derived in a series of biochemical reactions which involves the burning of sugar (glucose) in the foods animals eat with the oxygen they breathe. Normally when animals living on land, including humans, take a deep breath they inhale air containing 19-21% oxygen. From here on we will limit the discussion to humans, keeping in mind that similar activities, with variations in the details, also occur in other living organisms, especially mammals, the group of organisms to which humans belong.

The inhaled oxygen is not only dissolved in the bloodstream but it also binds to a molecule in the red blood cell called hemoglobin. The dissolved and bound oxygen is then transported through all of the blood vessels down to the tiniest capillaries. The bound oxygen is released, and along with the dissolved oxygen, diffuses to the individual cells of tissues and organs. Then the carbon dioxide, produced by the metabolism of the cells, is bound to the hemoglobin and transported to the lungs for elimination from the body.

THE AMAZING EXPERIMENT

Before discussing the transport of oxygen and its utilization by the cells, it is important to note that if the circulation is blocked such as it is in gangrene, myocardial infarction (heart attack) or in stroke, the consequences are deleterious. Even small reductions in blood flow will reduce the delivery of oxygen to the tissues and organs. Dr. Ite Boerema of Holland, in 1960, took a group of pigs from a farm and removed every drop of blood from them. He then substituted an artificial blood plasma to keep the circulation working and the heart pumping and put them into a hyperbaric chamber. Under hyperbaric oxygen conditions, even without a drop of blood, every organ functioned normally. Being frugal, he re-transfused half of the pigs and returned them to the farm. The other half were subjected to organ examination. Even with the total lack of blood there were no abnormalities in any organ: heart, lung, brain, kidneys, spleen, bone. This was an extremely important observation and showed clearly that life could be supported in a mammal without blood (red blood cells). This remarkable observation was very influential in the development of the field of hyperbaric medicine. It also introduced the use of hyperbaric oxygen as a substitute for blood transfusion to the Jehovah's Witnesses.

Let us now return to the release of oxygen from the hemoglobin in the capillaries. Each step in the process of transporting oxygen to cells is important. The last step, the breaking off of the oxygen from the hemoglobin and its subsequent diffusion to the cells and their utilization of it is very important. It is at these last stages that the cells are going to use the oxygen to convert the energy from glucose into a chemical compound that drives the life processes. This last step is energy laden.

THE CELLS

Cells are the building blocks of all living organisms. Each cell has a center called the nucleus containing the genetic information for building and repairing and functioning of the cells. The rest of the cell, the material outside the nucleus to the edge of the cell (the cell membrane) is called the cytoplasm (the liquid-gel portion of the cell). The cytoplasm contains essential sub-cellular structures (organelles); one of the most important being the mitochondria, where energy is obtained in a form that can be utilized by the cell.

THE CHROMOSOMES

The nucleus of every human cell (except the mature red blood cells which have no nucleus) contains 46 chromosomes (23 pairs); one chromosome of each pair is derived from each parent. The only other exception to the 23 pair distribution is the reproductive cells. The male sperm and female egg each contain 23 chromosomes. During fertilization one of the chromosomes from the mother pairs up with its corresponding chromosome from the father to produce a cell containing 23 pairs of chromosomes. Twenty two pair are autosomal chromosomes and one pair are the sex chromosomes. Each chromosome contains genes which direct growth, development and function of the human body.

THE GENES

The genes, located on the chromosomes are the basic units of heredity. One of the major functions of genes is to direct the synthesis of proteins. Thus, genes create proteins and proteins create us. Proteins are formed on the instructions found within the specific genes and consist primarily of amino acids. Proteins are the body's work horse, carrying out chemical structural function within the cells and on higher levels of biological complexity, tissues and organs. Like DNA and RNA, (to be discussed below) proteins are three dimensional. A faulty gene can create a misshapen protein which, in turn, alters its function.

DNA & RNA

Genes are composed of a complex chemical called deoxyribonucleic acid (DNA). DNA is the chemical basis of genetics and heredity. DNA is in the form of a double helix molecule which encodes the unique genetic blueprint of cells' individual traits. DNA is composed of four compounds called nucleotides. These nucleotides consist of two purine and two pyrimidine containing compounds. The purines are Adenine (A), and Guanine (G) and the pyrimidines are Thymine (T) and Cytosine (C). These four compounds fit together in a special way: The A always pairs with T. The G pairs with C. Any disarrangement of this complex puzzle may represent a misspelling of the message thereby sending wrong instructions to the cell leading to a mis-wired development or function.

Every human baby is 99.9% identical in DNA make up to every other human baby. It is the slightest deviation of only 0.1% that makes us unique individuals. In fact we are 98% identical in DNA to the great apes (chimpanzees). Even after billions of years of evolution we are 97% identical to the DNA in the yeast molecule. From comparative physiology and biochemistry we learn that what occurs in other organisms, especially on the molecular level of biologic

organization, may well occur in other living species as well. Thus, studies in yeast could profoundly influence our understanding of what happens in mammals, including humans.

RNA (ribonucleic acid) is an information encoded strand of nucleotides similar to DNA but with two slight changes; one of the pyrimidines, thymine, is replaced by a different one, uracil, and deoxyribose is replaced by a different five carbon sugar, ribose. DNA needs RNA in order to carry out its instructions. There are several types of RNA, each with a slightly different function. For example, mRNA (messenger RNA) mediates between DNA and proteins. tRNA (transfer RNA) works to line up the amino acids correctly. These amino acids are bound together to form proteins. The process of protein synthesis occurs in cellular organelles called ribosomes. Ribosomes are composed of protein and a third kind of RNA, rRNA (ribosomal RNA).

Genes are composed of segments of long DNA molecules which have their sequences transcribed onto messenger RNA, which then serves as a template for protein synthesis. Basically, DNA codes for the structure of messenger RNA, and mRNA codes for the structure of the specific proteins. Each gene is responsible for the structure of a specific protein.

In the 1990s another type of RNA, microRNA, was discovered. (The basic structure of DNA had not even been discovered until 1953). MicroRNA is a very short and unusual piece of RNA. Instead of synthesizing proteins, this tiny molecule latches onto messenger RNA, causing its destruction. Without messenger RNA no protein is produced. In effect the gene for that particular protein has been silenced. Micro RNA was originally thought to be an oddity or anomaly in a single species but has now been identified in various plants and animals - 200 in humans alone.

Protein production is a highly regulated process. The process of turning a gene on or off, depending on the cell's need for a particular protein, is called regulation of gene expression. Gene regulation is an essential part of life and is also critical for cellular response to metabolic needs. Since every cell in an organism contains the same genetic blueprint, different cell types are created by turning on and turning off different genes at different times during development. It is gene expression that allows stem cells to become unique cell types by being turned on ("expressed") or off ("silenced") in just the right combinations resulting in stem cells producing either heart cells, bone cells or brain cells, etc. The discovery of microRNA helps us to begin to understand these complex biological processes. It is now suspected that silencing particular genes at just the right times - a process called RNA interference - will push genetically identical cells down different paths of development, enabling some to perceive light while others digest food.

One of the important areas of research in modern biochemistry and developmental biology is learning about conditions and factors that turn genes on and off. In yeast it has been learned that oxygen is one of these factors.

THE MITOCHONDRIA & ENERGY SYNTHESIS

Oxygen is utilized in the cell primarily in the organelle called a mitochondrion (singular). Cells have many mitochondria (plural) depending on the specific function(s) of the cells and the amount of energy they require to carry out their functioning. Mitochondria are essential to every cell in the body. In 1963, it was discovered that mitochondria even contain their own genetic material (mtDNA) which is separate from the genetic material found in the cell nucleus (nDNA). Mitochondria are responsible for processing oxygen and converting the energy stored in the chemical structure of the foods we eat into a form that cells can use as a driving force for

all essential cell functions. Energy is produced in the form of a chemical compound called Adenosine triphosphate (ATP).

ATP is the universal currency of energy for all living organisms, i.e. all living organisms convert the energy in food to ATP. ATP is transported from the mitochondria to the cytoplasm (the liquid-gel portion of a cell) for its use in multiple cell functions.

MITOCHONDRIAL DISEASES

Mitochondrial diseases - now known as mitochondrial cytopathies - vary in clinical conditions depending upon the disturbance in the genetic make up of the mitochondria. Much information has been discovered since the 1940's and 50's when the first patient was diagnosed with a mitochondrial disease. Currently, there are over 40 known (identified) mitochondrial cytopathies. The main factor among these diseases is that the mitochondria are unable to completely burn the food with oxygen in order to generate sufficient energy (ATP) to sustain the integrated and coordinated functions of the cells and, thereby the functions of tissues and organs. These processes require numerous chemical reactions, all exquisitely coordinated, in order to have a continuous supply of energy to sustain life.

Incompletely burned food that accumulates may act as (a) poison(s) inside the body. These poisons can stop other chemical reactions that are essential for cell survival, making the energy crisis worse. In addition, some of these poisons can act as free radicals, highly reactive chemicals which readily form harmful compounds with other molecules. Free radicals can damage the mitochondrial DNA which has very limited repair abilities.

Mitochondrial diseases are classified according to the organ systems affected and the symptoms that are present. In certain cases only one organ is involved while in other patients multiple organs may be affected, and each system may have a wide variance of dysfunction. Depending upon how severe the mitochondrial disorder is, the illness may range in severity from mild to fatal. Mitochondrial cytopathies may affect any system of the body from the brain to the eyes, ears, gastrointestinal system, muscles, heart, liver, pancreas, thyroid, immune system, etc. or any combination of the above. This essentially creates an infinite number of manifestations of mitochondrial disease.

In the United States, by the age of 10, approximately 4,000 children will be diagnosed with or develop mitochondrial diseases. Between one thousand and four thousand children per year are born with some type of mitochondrial disease in the US.

Many diseases of aging have also been found to have defects in mitochondrial function in adults; including, but not limited to Type II diabetes, Parkinson's disease, arteriosclerosis, heart disease, stroke, Alzheimer's and cancer. It must be noted that many medications and toxins may injure mitochondrial function at any stage of life. In many patients, mitochondrial disease may be an inherited condition, i.e., it runs in families (genetic), with an uncertain percentage of patients acquiring symptoms due to other factors.

TYPES OF MITOCHONDRIAL DISEASE INHERITANCE:

AUTOSOMAL RECESSIVE INHERITANCE

Autosomal recessive inheritance may be the most common of the mitochondrial disorders. Remember that we all have two copies of every gene; one from our mother and one from our father. Only one of the two genes randomly enters an egg or sperm as it is formed. One gene from both egg and sperm results in the baby having two copies of that gene. In autosomal

recessive inheritance, both parents are carriers of the defective gene, but they each have only one copy. The parents are not affected because they also have a normal copy of the same gene. If both the egg and sperm carry the defective (bad, mutant) gene, then the child will have no working (normal) copies and will thereby manifest the disorder. Autosomal recessive inherited mitochondrial disorders usually result in severe disease with infantile onset.

Therefore, there is only a 25% chance that a child will inherit the defective gene from both parents and manifest the disease; (the same percentage applies to other siblings). Fifty percent of the children will inherit the defective gene from only one parent and will become unaffected carriers (like their parents) and 25% of the children will not inherit either copy of the defective gene.

AUTOSOMAL DOMINANT INHERITANCE

With dominant inheritance, only one copy of the defective gene is required in order for the associated disorder to develop; any child that inherits the defect theoretically should manifest symptoms of the disease. Occasionally this may not occur. In children who do show symptoms of the disease, the severity can vary markedly. Both autosomal recessive and autosomal dominant inheritance are similar in regards to the highly variable manifestations of the problems caused by the defective gene. If the trait is dominant, however, there is a 50% chance of it occurring in other siblings.

MATERNAL INHERITANCE

Both male and female children inherit their mitochondrial DNA (mtDNA) only from their mother, unlike the inheritance of nuclear DNA which comes from both the mother and the father. Maternally inherited mitochondrial disorders are not rare and possibly are as common as autosomal recessive inherited disorders. All mitochondrial disorders are maternally inherited.

While each of our cells contains exactly 2 copies of virtually every nuclear gene, each cell contains varying numbers of mtDNA copies, often several thousand per cell. People with maternally inherited mitochondrial disease may have any number of defective mtDNA cells. While one might assume that the more mutant mtDNA a cell contains, the more problems it will have; actually, the cell works quite well until the proportion of mutant mtDNA reaches a threshold (which varies among different tissues and by the nature of the different mutation)s. MtDNA inheritance has a more serious prognosis for the family than autosomal inheritance since there is a 100% chance of the trait occurring in other siblings, although the effects may be more or less severe. This means that the symptoms, severity, age of onset, etc., may vary tremendously within a family. Again, such variations could create an almost infinite number of manifestations. Unlike autosomal recessive inheritance, the onset of maternally inherited disorders is usually seen somewhat later in life, with the manifestations occurring anywhere from toddler age well into adulthood.

The combination of mtDNA and nDNA defects and their correlation in mitochondrial formation and function is as yet unknown.

The diagnosis of mitochondrial disease, at times, is extremely evasive and invasive; not to mention time and labor intensive and in most cases extremely expensive. A single muscle biopsy may cost in the range of \$26,000.00, so many insurance providers refuse to reimburse for this potentially important and powerful diagnostic technique, especially when it may require multiple biopsies for a specific diagnosis to be obtained. Some doctors and/or medical centers may even be unwilling to recommend this testing, since all mitochondrial diseases are thought to

be untreatable and are lump-summed into a vague category of incurable disorders for which the only treatment options are to try to ameliorate some of the symptoms, keep the patient comfortable, and/or to perhaps delay or prevent progression of the disease. Current treatment usually involves intensive vitamin and enzyme therapies along with occupational and physical therapy. The rationale seems to be that it is not worth the time, trouble or expense to specifically identify a disease which the medical community basically has no idea how to treat. Unfortunately, from a variety of perspectives, diagnosis thereby becomes irrelevant and unnecessary. It is often due to the parents' tenacity in pursuit of a definitive diagnosis that the more intensive tests are performed.

It is usually the "ruling-out" of the obvious simple causes of multiple, often extremely serious symptoms, that finally initiates the quest for a diagnosis of a possible mitochondrial disorder. Sometimes problems are noted by almost every doctor the child visits, i.e., neurologist, pediatrician, ophthalmologist or orthopedic specialist, etc. However, these observations may never be brought together into a coherent theory of diagnosis. It is especially true in the evaluation of the infant or child with the possible risk of mitochondrial disease that medicine should not be "cubby-holed" by specialty. I would therefore, urge all parents to discuss all aspects of their child's health with each medical professional; mention your child's change in vision or bowel/bladder habits to your child's neurologist and the ophthalmologist's or gastroenterologist's concerns to your neurologist or pediatrician. Hopefully, by so doing you will be giving all of them all a path of discovery into your child's problem.

Just as in any medical evaluation, diagnosis of mitochondrial disease begins simply with a family history and physical/ neurological examination of the patient. From that point, metabolic examinations will include blood, urine and spinal fluid tests (if necessary). If there is neurologic involvement, testing should include SPECT brain imaging to ascertain brain blood flow/metabolism or magnetic resonance imaging (MRI) to determine anatomic problems in the brain. Retinal or electroretinogram might be ordered for detection of a visual disorder and EKG or echocardiogram might be called for if cardiologic symptoms are present. Evoked potentials, which measure the nerve conduction from the brain back and forth to the eyes (VEP: visual evoked potentials), and the ears (BAER: brain auditory evoked response), may also need to be tested. Blood tests may be needed to determine thyroid function, and also to perform genetic DNA testing. The more invasive tests, such as biopsy of skin, muscle or brain, as earlier stated, are invasive and expensive, and are only performed as needed.

In this chapter we present one of the most complex mitochondrial disorders ever described with a totally remarkable outcome resulting from hyperbaric oxygen therapy. This is the case of little Gracie.

GRACIE

Mitochondrial cytochrome c reductase deficiency is an extremely rare condition. Only five cases ever diagnosed and cited in medical reviews worldwide could be found. Life expectancy is considered to be virtually zero. In four of the cases identified, the children died as infants (at < 15 months). The fifth case is Gracie.

Gracie spent the first year and a half of her life in hospitals being flown all over the country at an expenditure of over \$10 million dollars. She eventually had over 15 biopsies including tissue samples taken from brain, muscle and rectum. Gracie's final diagnosis was that she had a disorder of oxidative phosphorylation, a mitochondrial function. The intense vitamin therapy

program which allowed her to survive as long as she had consisted of sixteen vitamins that were given every two hours costing \$4,000.00 per month.

When first seen at the Ocean Hyperbaric Neurologic Center (03/28/02) Gracie was 3 years old, weighed 11 pounds and was diagnosed "failure to thrive". She was in a vegetative-like state, blind from optic atrophy, G-tube dependent, hypotonic, speechless, unable to crawl, unable to sit up and she lacked both fine and gross motor control. She had seizures and central apnea. Gracie had no sensation to pain and did not respond to touch or voice. There was severe cognitive deficit and she was physically and developmentally at an infant (3 months) stage.

Although we had never treated a case of this disorder (there being no other survivors), HBO is known to increase O₂ availability to the mitochondria and to have a positive effect on cytochrome c oxidase function when used as the primary treatment for severe carbon monoxide intoxication. On these theoretical bases, we agreed to attempt a trial of hyperbaric oxygen treatments for Gracie.

Prior to the initiation of hyperbaric oxygen therapy, a baseline SPECT brain scan was obtained at an independent institution. It showed a severe anoxic ischemic encephalopathy (AIE). This neurologic aspect of Gracie's condition had never been diagnosed before (as every other aspect of her health seemed to take precedence over concern with her brain function). Since hyperbaric oxygen treatments are a principle treatment of AIE, they were started immediately. Gracie's gradual physical improvement following 20 hyperbaric oxygen treatments was correlated with an improvement in her April 2002 repeat brain SPECT scan done at Joe DiMaggio's Children's Hospital in Hollywood, Florida. The radiologist's report states: "There has been a dramatic improvement in the appearance of the perfusion pattern to the brain."

Over a two month period Gracie received 63 hyperbaric oxygen treatments (1 hour at 1.5 ATA) and she began making surprisingly rapid developmental progress. She began to use her hands meaningfully. She learned to not only sit upright but to hold her balance and could pull up in her crib to standing. She began to say "Mama", "baba" and other meaningful vocalizations. She passed her swallow study, all nutrition was now being taken orally and she began to eat solid foods. The medications she was on for seizures, reflux and mitochondrial patterns were being tapered off. The intense vitamin program was no longer necessary as her body began to maintain these levels naturally, thus saving the family over \$28,000.00 (to date). All visual impairment disappeared and she began to see things and reach for them. A pivotal moment, says her mom was when the family was at a Greek restaurant and everyone began to throw plates to celebrate the ambience after the meal. Gracie actually reached out for a plate, grabbed it and threw it onto the floor like everyone else (with great delight, it might be added). Subsequently, two independent ophthalmologists confirmed no evidence of optic atrophy and confirmed that she now appeared to be, at least visually, a normal child. Hyperbaric oxygen treatments were continued. Final SPECT scans after 235 treatments (2/10/03) showed dramatic improvement with a complete normalization of all previous perfusion/metabolism deficits.

On March 20, 2003, after 238 treatments Grace's feeding tube was removed. Grace was on her way to a more normal life. The hyperbaricist and pediatric intensivist were of the opinion that with continued hyperbaric oxygen treatment and intensive physical, occupational and speech therapy, Gracie could reach limits never thought or dreamed possible.

Another muscle biopsy taken after 242 HBOT treatments (5/11/03) confirmed that Grace's muscle showed no evidence of cytochrome c reductase deficiency. As stated on the report by

Georgirene D. Viadutiu, Ph.D. at Buffalo Children's hospital: "No abnormalities were found among the enzymes analyzed. Succinate cytochrome c reductase moved from 14% in the respiratory chain to 82%. Medical genetics report states "Dramatic significant developmental achievements in the last 3 months coincident with treatment of hyperbaric oxygen therapy."

An important component of any assessment of the therapeutic efficacy, especially in young children, should include its impact on the family: This is what Gracie Kenitz's family had to say:

"Hyperbaric oxygen therapy has changed our whole life. We will be forever grateful for the people who believed that Grace should live, and who supported us in a decision that so many physicians were against.

We have seen so many changes in Gracie's life - ones we only dreamed of and never thought possible. Grace is catching up daily in her developmental milestones. She now responds to touch, voices and music. Our older daughter, Lily, now has a sister she can grow up with, and Gracie has grandparents who can spoil her, a father who looks to the day he can teach her to drive and someday walk her down the aisle on her wedding day. We are indebted to Dr. Raul Ponte, Grace's pediatric intensivist from St. Mary's Hospital, for stepping out of the role of modern medicine and telling us to try HBOT when most of his colleagues were against it, and to our hero, Dr. Richard A. Neubauer who is not only an exceptional physician but an extraordinary human being who gave us a glimpse of hope when so many others did not.

Because of HBOT our daughter can now laugh, smile and play - the three things that are so vital to childhood remembrance. HBOT gave us the opportunity to be a complete family again, to look into the future with hope and dreams instead of confusion and sadness. We now don't recall what we missed and lost with her in her first three years, but rather what we have gained from her such as unconditional love and joy and a future with unlimited possibilities. Grace is now age 5 and has had 384 hyperbaric oxygen treatments. On August 23, 2004 Grace will start kindergarten."

SUMMER

Summer was 4 years old when first seen in April of 2004. She was delivered at 36 weeks and stopped breathing twice during the process. At birth she was apneic (hypoxic). At one year of age she had 39 seizures in three days and developed apnea. The seizures started on one side of the head and progressed to the other. She finally had three types of seizures: grand mal, shuttering and staring. The mother was told at this time that Summer had heart defects and a liver abnormality. Summer ate a normal diet but remained very thin. She was given a working diagnosis of Angelman's disease. It remains highly frustrating to the family to later find that out that the symptoms for Angelman's and Leigh's were almost identical and that Summer's pattern of symptoms perfectly fit both diagnoses, yet she was only tested for one (Angelman's) and it was over a year later that she was finally tested and diagnosed with Leigh's. It was not until she was two years old that they could even arrange for the biopsy to discern the ultimate answer. The final diagnosis of Leigh's was made by a single muscle biopsy sent to Horizon Molecular in Atlanta in 2002.

Leigh's disease is a rare inherited neurometabolic disorder characterized by degeneration of the central nervous system caused by either mutations in the mitochondrial DNA or by deficiencies of an enzyme called pyruvate dehydrogenase. Symptoms usually begin between the ages of 3 months to 2 years and progress rapidly. The first signs may be poor sucking ability and loss of

head control and motor skills and may be accompanied by continuous crying, vomiting, loss of appetite and seizures. Symptoms may later include generalized weakness, lack of muscle tone and episodes of lactic acidosis, which can lead to impairment of kidney and respiratory function. Leigh's disease can also begin during late adolescence or early adulthood and progress more slowly.

It was initially thought that Summer might be developmentally delayed, although she could say over 45 words. The family had even started teaching her how to feed herself and drink from a regular cup, but within a two month period all of this progress disappeared. She could suddenly no longer feed herself, nor could she say a word. It was postulated that her brain processing had stopped and that she might from now on simply mumble a few words now and then. The doctors now felt that there was no hope and that her life expectancy would be 5-7 years. They told the mother that Summer would need a g-tube and trach and would probably die at home. The records showed that she was also diagnosed with atrial septal defect, and ventricular portal ductus arteriosus. The mother was told that the mitochondrial disease would attack every part of Summer's body.

When seen at the Ocean Hyperbaric Neurologic Center, Summer's medical evaluation noted hypotonia particularly in the hips and the legs, although she was very mobile and active. The heart defects had been surgically repaired in Atlanta. A VSD patch was in place and the cardiologist said that the leakage associated with the patch would eventually heal itself. A year prior to being seen at OHNC it was thought that she was having "break-through" seizures. Summer was hospitalized for a 48 hour EEG; yet there was no seizure activity. She did, however, suffer from insomnia; sleeping approximately two hours at a time and then staying awake and active for two or three days without a break.

When first seen she was on multiple seizure medications including Topamax (as well as Klonopin for sleep and Risperdal for ADHD). The last seizure, however, was 2-2 ½ years previously, yet the medications were continued even though Summer demonstrated a normal sleep EEG. She was also on Carnitor and CoQ 10 for mitochondrial disease and Zantac prescribed for GI problems. Although she remained very active and mobile, the main physical problem was still the hypotonia of the hips. She was flat footed with no arc, her upper motor coordination was poor, but weight was acceptable for size. Secondary diagnoses included epilepsy, sensory integration deficits and autistic behavior.

The results, following 19 hyperbaric oxygen treatments, have thus far been dramatic. Summer can now walk up and down stairs with one hand on the railing; something she had never been able to do before. In fact, she gets annoyed when someone tries to help her (which she absolutely needed before). Now it's "No, Mom, I do it!" and she runs up and down the stairs. She is learning to feed herself. Her speech is improving and she is saying meaningful 3-4 word sentences. Cognitive improvements include better understanding and response to commands. Her attentiveness is improving as she learns to use her visual skills and integrate them with her surroundings. She is being taken off the Klonopin at this point. Her basic coordination is greatly enhanced in activities such as pulling string toys and putting blocks in matching holes. Summer, for the first time has developed not only the ability but the initiative to do things like put her shoes and socks on by herself. The first time, admittedly, it was the right shoe on the left foot, but at least she put the socks on first. Small steps perhaps, but great leaps when you are a Mom.

BROOKE

The following is observations of Brooke's history prior to hyperbaric oxygen treatment in her Mom's own words:

"Brooke was born in April of 1999 via C-section at 32 weeks gestation, and had a twin brother. Brooke weighed 3.8 pounds at birth and stayed in the hospital 3 ½ weeks following birth.

Her development was slower than her twin in all areas, but was considered within normal limits by her pediatrician. She had two seizures in one day at age 5 months. She had another seizure a month later. She had a normal Brain MRI in September 1999. Her neurologist followed her for approximately a year and a half. When he dismissed her, he felt she would need no further neurological treatment.

All of Brooke's Well-baby check-ups were normal. At her four-year check-up, she was referred to a pediatric ophthalmologist. It was found that she had accommodative esotropia. She was prescribed glasses. She was also given her four-year immunizations (2 in the left leg and 1 in the left arm) at this check up in May of 2003.

Brooke was very verbal before she became ill, at times we complained that she talked all the time. In the latter part of May, after the vaccines, we noticed that she was drooling more than normal and her speech, at times, seemed to be strained. An even more dramatic development was that she didn't talk very much anymore. During this time frame, she vomited on several occasions with no apparent illness. She also felt a little warm from time to time, and people would comment that she felt like she had a fever.

Around the middle of June she had a bowel movement in our above ground pool; this was very unusual because she was potty trained at the time. We just assumed this was an accident (but now, we're not so sure). The last four times she got in the pool, she had a BM in her swimsuit. When asked why she did not tell us she had to go, she said, "I was in a hurry", or "it was an accident". Also while riding in the car she would suddenly announce, "I wet my panties". I don't think she can control her kidneys and bowel functions at this time.

Later in June, she started really having trouble with her speech. Her twin had gone through two spells of stuttering that were short lived, so we assumed that's what was going on with Brooke. It was as though she knew what she wanted to say but couldn't get her words out.

One day in July of 2003, she got up and couldn't bend her left leg. She was walking stiff legged. We panicked and took her to her pediatrician's office. He said he felt some clonus in her left leg/ankle and referred her to a pediatric orthopedist. Her appointment was two weeks later. The only thing we mentioned to him was her walk. We didn't realize the other issues could possibly be related. He looked at her history and told us he thought she had a mild case of cerebral palsy. We were devastated. He referred us to her previous neurologist, but as it was two weeks before she could be seen, we asked for an MRI of the brain so that we could have the results before our appointment. This was done. It was at least four weeks from the time we noticed her awkward gait; her condition was worsening and she was receiving no treatment, however, she did begin physical therapy for CP. It was during this time frame that her hands and arms began to shake when she tried for fine motor control in the act of picking up anything. On August 21, 2003, we returned to the neurologist. He immediately told us that it was not CP, but that her brain MRI was "very disturbing". He admitted her to Scottish Rite Children's Hospital the next morning. They performed a spinal MRI, spinal tap and numerous blood test and had a pediatric ophthalmologist look at her. The neurologist told us that the best case

scenario would be an encephalitis or brain inflammation. He also told us that he could not rule out a metabolic or mitochondrial cause. He informed us that he would treat her with IV steroids for a 5 day regimen. He stated that if she responded to the steroids, it would be a good sign and that hopefully it was only an inflammatory problem. The steroids were started that day. By the next morning, her speech had improved tremendously, and during the course of the steroids, she continued to improve. Her neurologist had by then called a geneticist in on the case. She told us that since Brooke had responded to the steroids, she didn't think we needed to do the genetic testing at that time. She told us to call her if Brooke didn't improve. Brooke was released following the five day steroid treatment and went home on a steroid weaning schedule.

Back at physical therapy, her therapist was very impressed. She said that Brooke's tone had decreased from 80-90% to 10% and that the clonus was almost gone. Brooke continued to progress, but slowly. Two days after she was completely off the steroids she began regressing. Her gait worsened as well as her speech and drooling. Now the neurologist stated, "This is not encephalitis." He also said that it was more like a bulbar myelitis. He stated that he did not know what was wrong with her; he had no definite diagnosis. He started her on Prednisalon twice a day; 5 ml in the morning and 5 ml at night. He told us we would wean her off over a 10-week period or so. He said if she continued to progress; great. If not, the next step would be a muscle biopsy. She continued to progress; for awhile.

I had been noticing that her urine was very cloudy, and thought the steroids were probably causing it. I called the doctor's office to see if that could be the case. They told me no, the steroids shouldn't cause it. I was told to bring her in for a urine test. They found white cells and blood in the urine. They sent me home with two samples of the antibiotic Cefzi., They told me they would culture it, but they felt sure she had a urinary tract infection. To everyone's surprise, the culture was negative, so nothing further was done. That afternoon about 1:00 Brooke started complaining of stomach pain. We were on the way to physical therapy, so I guess she was preoccupied and forgot about it. By 4:00 she was doubled over complaining of pain in her right side. I took her back to the doctor's office. He said her white cells were 12,000 (8,000 is normal). He sent her to the Medical Center of Central Georgia for an abdominal x-ray. Once we got to the hospital she got much worse and vomited 5 times in an hour time frame. She was very shaky and still doubled over with pain. They did another white cell count and it had skyrocketed to 27,000 (while another test done at 5:00 a.m. the following morning revealed a count of 11,000). She was admitted with appendicitis in mind. At his point, Brooke was very unresponsive to everything and everyone. Surgeons came in and decided that it probably was not appendicitis but wanted to watch her overnight, and order a CAT scan if warranted. It was decided that the CAT scan was not needed. Although they had no diagnosis, appendicitis was ruled out. They did find that she was dehydrated and gave her two bags of fluid. She was better the next day and no further testing was done. They started her on 2 broad-spectrum IV antibiotics. The urine they collected at the hospital was cloudy. The nurse even commented on it. The nurse told me it had white cells and protein in it. However, the attending doctor said it was fine. The culture was negative. She was released from the hospital about 6:00 p.m. on October 17th again with no diagnosis.

On October 12, just prior to her hospitalization, her therapist had been quite pleased with progress. She then had good balance (for her), and was able to walk the balance beam while holding the therapist's hand. After this latest illness, however she continued to regress. Her balance worsened to the point that she could not walk without holding on to someone or something. When she took two or three steps on her own, she would veer to the right and could not walk in a straight line.

By now the shaking of her hands and arms was at times uncontrollable and she would drop what she was holding. Much of the time she could not even pick up a glass or feed herself because of the shaking.

On the afternoon of October 25, while trying to get her Papa to sleep, after a few minutes of silence she said, "Papa, I can't walk." Her mind is very keen and she knows exactly what is happening but she is slow in phrasing her thoughts and responding. However, she is very quick to grasp what is going on. Unlike most four year-olds, Brooke worried about her condition and all that was happening.

I called and talked to the neurologist (on call) on October 25. I explained most of the above and told him that Brooke will not (or cannot) walk on her own, she has to hold on to something or someone to ambulate; that this was frightening and worse than before. Brooke was once again admitted to the hospital. By this point we were desperate for answers and a diagnosis." Finally, a muscle biopsy was performed and it appeared to be a mitochondrial disease, most probably Leigh's.

When seen at the Ocean Hyperbaric Neurologic Center in January of 2004, the mother stated that Brooke, now 4 3/4 years old, had continued to deteriorate. She could no longer talk at all. She could no longer walk, turn or crawl. In appearance, she was a well-developed, well-nourished child with a slight "moon face" secondary to the cortisone. She was small and very alert, but was unable to express herself in any way. Both lower extremities were positive for low grade clonus with slight clonus of the right hand. There was generalized severe weakness of all 4 extremities. She could not hold her head up nor her torso erect. Baseline SPECT brain scan revealed multiple areas of hypoperfusion and patchiness indicating decreased blood flow and thereby limited oxygen metabolism. The patient was begun on hyperbaric oxygen treatments at 1.25 ATA concomitant with all standard modalities of PT, OT, and speech therapy. Following 74 HBO treatments, repeat SPECT scanning demonstrated significant improvement in the cerebral cortical flow. The previous occipital defects had disappeared and these regions were now well perfused.

As of April, 2004, she had received 78 hyperbaric oxygen treatments with dramatic results. Brooke is now back in school. She is walking and feeding herself and continues to improve. Her speech and mentation have improved and she is now speaking in full sentences and continues to improve cognitively. Brooke now takes steps independently and can bend her knee; neither of which she was able to do prior to the hyperbaric oxygen treatments. Brooke is able to control her bowel/bladder independently and is now consistent with her bowel movements. Emotionally, she is able to giggle and laughs appropriately; in fact, she has quite a sense of humor. Her parents report that her overall stability is becoming closer to normal and both her independent neurologist and physician feel that the hyperbaric oxygen played a definite role in her amazing progress.

CONCLUSION

Explanations for the phenomena herein observed on the admittedly few cases of mitochondrial cytopathies treated with HBO remain somewhat elusive, but the most likely conclusions are that hyperbaric oxygen exerts a positive effect on the mitochondria in their production of ATP, utilization of glucose, amino acids, oxygen and cell respiration. HBOT apparently rectifies certain problems in the mitochondrial function by either increasing cytochrome production, altering the structure of proteins or increasing the efficiency of the cytochromes already present.

In all probability it also has the ability to selectively turn mitochondrial genes on and off. The emerging understanding of the mechanisms of HBOT in treating mitochondrial cytopathies is generating new and exciting concepts for the use of the ever expanding field of hyperbaric oxygenation in the treatment of the brain injured child.

Addendum:

With more recent scientific evidence in mitochondrial studies and imaging, multiple diseases are now linked to mitochondrial failure not only in children, but also adults in the liver, cardiac, renal system and brain (including Alzheimer's, etc.). Previously mentioned was the recognized effect of carbon monoxide on cytochrome c, but a recent paper in the Journal of Neurosurgery (2004) clearly shows the effect of mitochondrial damage in traumatic brain injury in the experimental animal. This parallels the work with hyperbaric oxygen that that we have been doing for years in humans and the logic of this approach becomes even clearer.

Mitochondria, however, is its own worst enemy. Organs which require more energy (brain, heart, etc.) have more mitochondria and are more susceptible to its damage. Electron transport, hydroxyl radicals and reactive oxygen species (ROS) are routinely formed as basic mechanisms of the cell, yet they tend to destroy the mitochondria. The body has produced mechanisms to try to defeat this with UCP (uncoupling) enzyme which has recently been found to have been a basic defense in both animal and plants for centuries. When they are released, ROS supercedes mitochondrial function. Mitochondrial failure results in many disease states, and is even found in the basic human aging process. Thus, mitochondrial disorders are not simply limited to inherent genetic diseases in children. This is a whole new field of medical research and this chapter is the first publication to suggest that hyperbaric oxygenation may indeed turn on good genes, turn off bad genes and positively alter and enhance the function of the mitochondria and the production of ATP.

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