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Unusual Presentations of Mitochondrial Disease

by Jessica Hilliard

I stared at the floor after the doctor finished speaking. From the corner of my eye, I gazed distractedly at the growth chart clutched in my right hand, trying to collect my thoughts. It was a standard pink and white "Girls Newborn to 3 Years" chart, dotted with tiny black points showing weight in relation to age. Try as I might to assemble an intelligent response to the doctor's comments, my mind kept hiccupping as my eye caught the pattern of data on the chart. From top to bottom the page was filled with sweeping curves; a multitude of rainbows demonstrating the proper way little girls should grow and gain weight. But like single-minded insects, the dots representing *my* daughter's "growth" marched downward toward the bottom of the page, ignoring the clearly marked paths. A bad headline, the words, "Failure to Thrive," had been written in sloppy red letters at the top of the chart and circled by an unknown specialist.

At nine months of age, the nutritionist had noticed a lack of growth and weight gain, and simply shrugged, commenting that we should restart the nighttime feeds of formula we gave her directly into her intestines via a feeding tube. At 12 months we switched formulas and increased calories, but weight gain was nil, and pain with feeds was becoming regular. By 14 months we had switched formulas again, and discovered that severe hypoglycemia was setting in anytime tube feeds were stopped. Pain was constant, but the need for calories and blood sugar stability prevailed over comfort. Six months later in the office of yet another specialist, my 18-month-old weighed less than she did at nine months. Despite a slew of medications and a round-the-clock drip of high calorie formula, my daughter's gastrointestinal pain was constant, her blood sugars unstable, and all of our interventions were failing.

"Severe Failure to Thrive" was added to a growing list of frightening problems that had suddenly cropped up over the last year. Our urgent need for help was as incontrovertible as the line of black dots running across the growth chart in a terribly wrong direction.

Too Many Diagnoses

That morning I had braved a doctor in the metabolism department, hoping to hear that--at last!--my daughter's symptoms all made sense. For months I had been carefully observing and documenting each new medical problem as it appeared. Using my college training in biochemistry, I went to work combing the medical literature, and came up blank. There was no one like her at all. Still, after gathering a few applicable pieces of

research, and multiple prolonged conversations with both specialists and other parents of children who are medically complicated, I was fairly certain my little girl was fighting an underlying metabolic disorder. Specifically, I believed it was a Mitochondrial disorder.

I was no doctor, but I felt the evidence was compelling enough to at least warrant consideration, and probably testing. No one else seemed to agree. Doctor after doctor reviewed the three typed pages of diagnoses, the multitude of carefully organized labs, reports from months spent in the hospital, and the reams of clinical notes clearly documenting clinical progression consistent with Mitochondrial diseases. One and all, they simply shook their heads: "It's just not *possible* for Eithene to have a Mitochondrial disease."

Admittedly, our presentation was an unusual one. Instead of a lack of medical information, my daughter Eithene simply had too *many* problems. Although many new problems had plagued us her second year of life, we had known from 18 weeks gestation that her medical course would be long and involved. Weekly ultrasounds revealed a

growing list of serious birth defects, and we were told to expect the need for multiple surgeries throughout her life. Within a week of birth, Eithene had already earned herself three life-saving surgeries and a frightening diagnosis: VACTERL Association.

A rare congenital birth defect condition, VACTERL Association can affect more than seven different organ systems, resulting in missing organs and life-threatening deformities. Eithene was born missing a kidney, with her colon, vagina, and bladder fused, and with her trachea connected to her esophagus. These are just a few of more than 15 serious problems. We cried and worried for her future, but the doctors had some encouraging news. VACTERL was scary, but it was not genetic. It did not get worse over time, and the problems were usually corrected or stabilized by the age of two years. We were told our job was to help Eithene survive the multitude of surgeries she would need in her first few years, and then to relax and watch her grow up with a few special needs, but still as a "relatively typical" little girl.

Surviving her birth defects was no easy feat, but as Eithene's second birthday approached, doctor and parent alike began to anticipate the promised relief from the medical storm. It never came. Even as Eithene's surgical problems stabilized, she began to develop a troubling list of non-VACTERL issues. Heart rates, blood pressures, and temperatures became increasingly unstable, scaring her nurses and doctors. Her motor skills failed to progress, and she kept regressing in her speech skills. Her reflexes slowly disappeared, and her GI tract began to shut down, resulting in failure to thrive with severe hypoglycemia.

Nothing made sense. These issues were clearly not related to VACTERL Association, but the "usual suspects," progressive neurological or metabolic conditions, were ruled out due to the existence of her birth defects. Doctor after doctor proclaimed that yes, something was *very* wrong, but since VACTERL was not often associated with other disorders, they couldn't make a diagnosis. VACTERL *certainly* was not associated with metabolic conditions like Mitochondrial disease, so that couldn't be our answer!
As Eithene was quite sick, she was given a world-class work-up for practically every other disease known to modern medicine, but it was deemed pointless to pursue testing for metabolic conditions beyond a round of easily obtained blood and urine labs. When these proved normal or inconclusive, all metabolic testing was ordered stopped. Our geneticist told me that she definitely didn't have Mito, and we would never know the source of her progressing health issues. I was nicely advised to stop looking for the "unifying diagnosis," and to just focus on keeping my seriously ill toddler alive.

Connecting the Dots

For the next year I did just as advised, but I never could shake the suspicion that Mitochondrial disease had my daughter in its ruthless grip. By age 2.5, Eithene's problems had progressed to the breaking point. Seven months earlier she had been rushed to the ICU with severe hypoglycemia. Her failing GI tract would not absorb the sugar we kept bolusing over and over. She was taken off all enteral feeds and given IV

nutrition for a month while her doctors argued over how to proceed. Different options were considered, but eventually her lack of a unifying diagnosis overshadowed everything else. The doctors kept coming back to the fact that there was "no reason" for a child with VACTERL to have intestinal failure, and we couldn't find any other diagnosis. We were told that she probably didn't have true intestinal failure, and we just had to keep feeding her and assume her non-VACTERL problems would eventually resolve. IV nutrition was stopped, and we were assured that her GI tract would start to work again.

As the months crawled by, Eithene began to lose function in multiple organs and other body systems. Her GI tract did not restart working, and like her other systems, continued to decline. We were overcome with watching our daughter deteriorate piece by piece. At 32 months, she was eight kilograms, the size of an infant. She was seriously malnourished and in terrible pain most of the day and night. She did not sleep, did not smile, did not play, did not walk, and did not interact with us much except to cry or complain of pain. All of her earlier frightening problems had continued to progress as well. The majority of her doctors were as horrified as my husband and I at the terrible transformation that had occurred, and agreed that a progressive neurological or metabolic process truly seemed to be at work. The feeding trials were stopped and IV nutrition restarted, and then neurology strongly advised our reluctant metabolism team to finish the testing for Mitochondrial diseases. Unlikely or not, we had ruled out every other disorder we could think of and Mitochondrial disease was all that was left.

Nine months and multiple tests later, I found myself once again in front of the metabolism team attempting to compose my thoughts. This time the piece of paper distracting me was the report from her muscle biopsy. A sentence at the bottom of the Electron Transport Chain report read, "Complex IV (Cytochrome C Oxidase)....*Severely Deficient."* Eithene had finally found a diagnosis accounting for her progressive organ failure: Cytochrome C Oxidase Deficiency, known informally as "Mito Complex IV."

She did indeed have a form of Mitochondrial disease. I was overcome by a multitude of thoughts. "I can't believe we finally found it!...Why did it take so long to diagnose this?…What can we do now?"

As anyone who has walked this path can say, the diagnosis of a Mitochondrial disease means both everything and nothing. There are no cures, and no proven treatments. There was no "magic pill" we could have given Eithene two years earlier had we known about the Mito, but there *were* treatment decisions we could have--and *should* have--made. For instance, proper nutrition and hydration are of utmost importance for children with Mitochondrial diseases. Had we known about the dysfunction in her Mitochondria, we would never have allowed her body to go months without nutrition or adequate fluids as we did during the feeding trials. I consider it a gift from God that the skills and functions she lost during that period came back once IV nutrition was restarted. For many children with Mito, such restoration would not have been the case. Looking back, I consider it grace in general that many of our interventions done under the assumption of dealing with "only VACTERL" didn't kill her.

Awareness and Research on Unusual Presentations

As awareness began to grow of how our lack of a diagnosis had affected Eithene, I found an equal determination to smooth the path for others. My daughter is treated at a world-class children's hospital. None of the specialists we saw were simply stubborn or uncaring when they decided not to consider a Mitochondrial disease for Eithene; they truly found the idea unreasonable. "Mito" is a young disease in the medical world. Until recently, studies on even well known primary Mitochondrial diseases were few and far between. Little is known, and less is written, about either atypical presentations of primary Mitochondrial diseases, or the vast array of serious secondary Mitochondrial disorders.

Moreover, diagnosing a Mitochondrial disease is known to be difficult, time consuming, and invasive. Historically, many doctors have been reluctant to pursue extensive testing even when the symptoms of Mito are fairly straightforward. If you add in unusual complicating problems like multiple birth defects, hard evidence in the form of published research is needed to convince doctors that the testing for Mitochondrial dysfunction is reasonable. Eithene's presentation was highly unusual, and the biggest reason Mitochondrial diseases were absent from her diagnostic differential was lack of medical research about others like her. Was she truly unique? Or had other families simply failed to make headway in diagnosing Mito where we had prevailed?

I have little influence over the realm of academic journals, but I did what I could to promote awareness about our struggles amongst our doctors and in parent groups. After hearing about Eithene's diagnosis of Mito, several families from the VACTERL community approached me. They related that their children were also suspected of having Mitochondrial diseases, but diagnosing the issue had proved incredibly difficult for many of the same reasons we encountered. One family knew a specialist in Mitochondrial diseases who was open to the idea of a link between VACTERL and Mito, and who claimed to have treated several patients with both disorders. I knew of a researcher at the National Institute of Health (NIH) who was interested in unusual VACTERL cases. Along with a few other families, I wrote to the NIH and asked their researcher if he would be interested in investigating the unusual disease afflicting our children with both birth defects and metabolic issues. Shockingly, he was not only interested, but also adamant that a study be done! He personally contacted the specialist who had seen children with both Mito and VACTERL, and before we knew it, they began collaboration for a brand-new research study into VACTERL association and Mitochondrial dysfunction!

A Devastating Disease

At almost four years old, Eithene deals with a multitude of medical problems, including complete intestinal failure, autonomic dysfunction, a bone marrow disorder and much

more. Hardly a system in her body remains unaffected by her disease process, and it seems we discover another problem every month. We still don't know if our daughter's Mitochondrial disorder is primary due to a genetic defect in the genomes controlling Mitochondrial function, or secondary to a completely different undiscovered disease.

I can't foresee what conclusions the NIH study may yield about the connection between VACTERL Association and Mitochondrial Diseases, and I can't say if the results will come fast enough to benefit my daughter in her lifetime. I *can* say that this study is a big step toward greater understanding about unusual presentations of Mitochondrial disorders. I can also tell you how relieved I am to have made even that small difference, because our story is only one of many.

According to the United Mitochondrial Disease Foundation, every 30 minutes a child is born who will develop a Mitochondrial disease before the age of 10.[1] Due to the lack of knowledge about Mitochondrial diseases, many of these children will be misdiagnosed with a different disorder, or remain undiagnosed until after death. The latest research indicates that the true number and variety of Mitochondrial disorders is likely staggering, as Mitochondrial dysfunction is already indicated in diseases such as Parkinson's, migraines, solid tumor cancers, Alzheimer's, certain forms of Autism, and many, many others. Promoting research into all aspects of Mitochondrial function and dysfunction is key to advancing our general medical knowledge, because as many as 1 in 200 people carry a mutation that could develop into a Mitochondrial disease, and over 50 million in the US alone suffer from chronic diseases already known to involve Mitochondrial problems.[2]

But, while the battle just to identify the majority of Mitochondrial disorders is far from over in the world of research, it is only a prelude to an even bigger war: the fight for treatments and cures. Until we have the knowledge to treat Mitochondrial dysfunction, Eithene and many others fight for their lives every day against a foe they cannot defeat. As many different papers as I've held throughout the long course of my daughter's medical adventures, I am still waiting to hold the most coveted of them all: the paper that reads, "Mitochondrial disease: *Cured*."

Jessica Hilliard lives in Massachusetts with her husband Sean, and two children Eithene and Gabriel. Eithene was diagnosed with VACTERL Association at birth, and Mitochondrial disease in November 2009. Jessica shares the challenges facing her family as they deal with Eithene's life-threatening illness in her blog www.fromthebanksofjordan@blogspot.com.

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[1] http://www.umdf.org/site/c.otJVJ7MMIqE/b.5692895/k.B04C/FAQs.htm
[2]http://www.umdf.org/site/c.otJVJ7MMIqE/b.5692893/k.6478/Links_to_Other_Diseases.htmv