Summary – Immunodeficiency Disorders and Mitochondrial Disease

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Introduction Dr. Pacheco is a pediatrician who specializes in pediatric immunology at Memorial Hermann Texas Medical Center in Houston, Texas. She works with Dr. Mary Kay Koenig, Neurologist, in the Mitochondrial Center of Excellence. Dr. Pacheco's interest in the field began many years ago when she noted that there was very little research in the medical literature about immune function in those patients with mitochondrial disease. She now has begun a systematic evaluation of the immune status of patients with mitochondrial disease, which up until now has not been documented in the medical literature. Her discussion will focus on the treatment of children with infections and immunodeficiency who also have mitochondrial disease and can be supplemented by following along with the slides available on the MitoAction website.

The objectives for this discussion are:

- *Explain why we should consider immunological problems in children with mitochondrial disease*
- *Provide basic guidelines for the evaluation and treatment of infections and potential immune problems in children with mitochondrial disease*

The Immune System & Mitochondrial Disease We know that the hallmark of mitochondrial disease is a lack of ATP production. This affects all organs, but particularly those with high energy demands (gut, muscles, brain). In mitochondrial disease the body struggles to balance energy needs with energy production. It is notable that a description of mitochondria and immune function is **absent** from all major reviews and textbooks on mitochondrial medicine published so far. This is true, even though severe, often fatal, infections occur in individuals with defined mitochondrial symptoms like MELAS, Pearson's-Kearns-Sayre overlap syndrome, and infections with unusual pathogens like Aspergillus. In the general population, when we encounter children with infections, we evaluate them for immune dysfunction to see if there is a relationship. Now, especially at Dr. Pacheco's center, they are looking to see if there is a connection between immune function and Mito disease. So far over 50 patients have been evaluated.

When an infection begins, it triggers the immune response - a prolific and dynamic activation of the immune system. T cells are the captains or directors of this response and begin a nonspecific but complex battle which activate and proliferates chemicals which directly attack the invading microbes. B cells, on the other hand, respond with more specific immunoglobulins in response to the specific infection. This activity is rapid and calls up thousands of cells, therefore, requiring a lot of energy. We know that patients with Mito are constantly balancing energy needs with energy demands. When disequilibrium occurs from the increased energy demands, Mito patients may exhibit

tissue dysfunction based on these energy demands. These dysfunctions can range from GI dysmotility to developmental delays or myopathy (see slides). For example, children with Mito who are receiving TPN may not be able to mount the defense needed to combat infections due to the increased energy this demands. Data from the patients being evaluated in Texas show that 98% of patients report that infections take longer to resolve than "normal." Also, 94% report recurrent, severe or unusual infections (see slides).

What we think is happening The research at UT is still in the early stages but preliminary data seems to suggest the presence of immune dysfunction in children with mitochondrial disease. Specific data which is pictured on the accompanying slides show increased number of catheter associated bloodstream infections with sepsis in those with Mito. It may be that these children initially have normal immunological function then present rather quickly with severe infection. This drop in immunoglobulin level may be related to mitochondrial disease in that the immune response requires so much energy and the body just cannot produce the needed energy quickly enough. This certainly requires more study.

Primary Immune Deficiency is identified by "a family history of immunodeficiency, use of IV antibiotics for sepsis in children with neutrophil PID and failure to thrive in children with P-lymphocyte PID."(Subbarayan 2010). Dr. Pacheco does not know if children with Mito have primary immunodeficiency or if it is a result of energy production issues; more research is needed. It is important to note the 10 warning signs of Immune Deficiency and to track them in Mito patients.

10 Warning Signs of Immune Deficiency

1) 4 or more new ear infections within 1 year
2) 2 or more serious sinus infections within 1 year
3) 2 or more months on antibiotics with little effect
4) 2 or more pneumonias within 1 year
5) failure of infant to gain weight or grow normally
6) recurrent deep skin or organ abscesses
7) persistent thrush in mouth or fungal infections on skin
8) need for IV antibiotics to clear infections
9) 2 or more deep-seated infections including septicemia
10) a family history of Primary immunodeficiency

Because Mito patients do not fit the picture of those with primary immunodeficiency, we need to continue to study the connectedness of these two issues.

What are we doing? At the University of Texas Medical Center, a comprehensive, multidisciplinary approach is being used to evaluate all Mito patients for their immune status. All patients are screened for potential immune deficiency and are monitored closely for infections. Even those whose immune system evaluation appears normal can have a rapid and severe decompensation of their immune system if/when they go into a

crisis.

In addition, testing of immune factors is recommended when patients are initially evaluated in order to obtain a baseline; at this time they may be well and have an intact immune system. However, during a period of metabolic stress, the immune status should again be tested. Sometimes the changes may only be subtle - a slight change in WBC, but this is important data.

Many patients who enter the Texas Center in crisis go to the PICU where they can be carefully evaluated and treated. A normal immunoglobulin level can fall rapidly because of low ATP production and make one much more prone to infection. Prompt assessment and treatment of any metabolic decompensation and or infection is undertaken and aggressive treatment to any and all infections is taken. Treatment of infection is aggressive and the vast array of available antibiotics can be used (except those known to be Mito toxic).

IgG values are also taken and children on parenteral nutrition or with GI dysfunction with prior septic episodes will be treated with immune prophylaxis. Other prophylactic treatment is also recommended (i.e. vaccines and immunizations for influenza and pneumococcus). Mito patients prone to infections can also be pretreated prior to surgery to prevent post-surgical infections. Additionally, Tamiflu is recommended for those who come in contact with someone with influenza. Sometimes immune prophyaxis is considered for Mito patients who are receiving parenteral nutrition or those who have GI dysfunctions because of the evidence of higher incidences of infection. Intravenous gamma globulin can be given or SC injections. All of this needs to be done with great consideration and care.

Those wishing to contact the Texas Medical Center can do so at: UT.MITO@UTH.TMC.EDU or www.UTMITO.ORG or 713-500-7164.

Summary There is a need to continue this research and to share what is learned with patients, families, and physicians. The "normal" immune system in patients with mitochondrial disease may become compromised when energy demands increase. For this reason, immunizations, vaccines and aggressive treatment of infections need to be used for Mito patients. Awareness of when metabolic decompensation may occur and the possibility of a concurrent increase in infections is also necessary. In other words, there needs to be an increased awareness of the potential for immune system changes in all Mito patients. Precautions like careful hand washing, use of hand sanitizers and avoidance of those with infections and contagious diseases continues to be very important for preserving the fragile baseline of a child or adult with mitochondrial disease.

Submitted by
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