workshop b3: saturday, march 11

Clinical Issues in Mitochondrial Disorders

Clinical presentation and management in children with mitochondrial disorders.
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Although there is no widely accepted consensus, for the purpose of this presentation clinical mitochondrial disease is defined by a triad consisting of 1) clinical manifestations (usually neuromuscular and/or multisystem dysfunction), 2) biochemical signs of abnormal energy metabolism (elevated body fluid lactate and consistent abnormal urine organic acids), and 3) the lack of another diagnosis after a complete work-up. In our experience at Childrens Hospital Los Angeles, children fulfilling the above criteria almost always have abnormal muscle biopsies, usually mitochondrial proliferation and lipid storage. Although only a small minority of these children have a definable abnormality on the genetic or protein level, in the majority the clinical manifestations are similar enough to be considered syndromic, suggesting a single pathophysiological mechanism. In our clinical experience, anticipatory guidance regarding potential future complications has a positive role in the care of these children. Many of the common complications are debilitating and difficult to diagnosis, but are readily amenable to specific treatments once recognized by the parent or physician.

Although migraine headaches are well described as part of mitochondrial disease, the scope and range of transient "migraine-like" neurological dysfunction is generally unappreciated. In addition to headaches, other symptoms such as abdominal pain, cyclic vomiting, muscle cramps, and neurovascular dystrophy are common. These symptoms can be severe and debilitating, and often occur in the same subset of patients who may present with one or any number of the above symptoms. In most cases, these manifestations are found in children with normal or near-normal intelligence and with matrilineal inheritance patterns. In each of 15 cases treated (non-blinded) to date, these manifestations resolved upon treatment with one of the "anti-migraine" agents amitriptyline, cyproheptadine or propranolol. The use of caffeine is often helpful if given at the onset of symptoms. Gastrointestinal dysmotility is found in over half of children with clinical mitochondrial disease, and often responds to symptomatic therapy. Pancreatitis, absence seizures, hypothyroidism, growth hormone deficiency, renal tubular acidosis, and hearing loss are additional treatable, yet often cryptic, complications. Finally, a subset of these children develop an anion gap metabolic acidosis upon fasting which occasionally results in permanent brain damage. Susceptible children usually manifest intermediates of lipid metabolism in the urine, but false positives can occur in an anabolic state. Prophylactic treatment with 10% dextrose containing fluids during gastroenteritis and in the peri-operative period prevents this potential complication.

Options and Challenges in the Treatment of Mitochondrial Disease.
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Effective pharmacologic therapies of mitochondrial disease have been limited because of our rudimentary, albeit rapidly expanding, knowledge of the many roles mitochondria play in the metabolism of differentiated, non-growing cells. Biochemical tests of growing cells in culture do not predict the symptoms observed clinically in patients with mitochondrial disease. Mitochondrial function is not limited to energy production. Mitochondria are required for the synthesis of hundreds of chemicals that are absolutely required for the normal function of all organ systems. State-of-the-art therapy for mitochondrial disease in children starts with a comprehensive metabolic and nutritional evaluation, and the design of a diet tailored to the individual needs of the child. The diet is designed to minimize lactate and other organic acid production and to optimize growth. In both children and adults, balanced supplements of mitochondrial cofactors (CoQ10, B-vitamins, folate and biotin) are routinely provided, although rigorous evidence for significant efficacy has been difficult to establish. Chronic antioxidant therapy is likewise controversial in congenital mitochondrial disease, because these patients already have an excess of intracellular reducing potential. Carnitine is used when a documented deficiency is established. Dichloroacetate (DCA) is sometimes used to lower blood and cerebrospinal fluid lactates. However, in our series of 50 patients with congenital lactic acidemia, only about 25% of patients show clear-cut clinical benefit. Some patients appear to deteriorate when lactate is reduced and make recoveries when the lactate is permitted to rise to moderate levels. In addition, about 5% of patients have a paradoxical response in which lactate levels rise in response to DCA. An emerging modality of treatment is pyrimidine therapy. Triacetyluridine (PN401) is a prodrug of uridine that is rapidly absorbed and converted to uridine. Normal oxidative phosphorylation is required for *de novo* uridine synthesis. A pilot study of PH401 treatment of mitochondrial disease has demonstrated clinical benefit in up to 50% of the patients, and has led to improvement or correction of renal tubular acidosis in 4 of 4 patients studied with mitochondrial RTAs

Precision and uncertainty in mitochondrial genetics: clinical approach and a parent's perspective.
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A case of mitochondrial DNA deletion resulting in multisystem dysfunction is discussed to bring out the well-known uncertainties inherent in the biology of these disorders. The presentation, reminiscent of Rothmund-Thomson Syndrome, as well as subsequent progression of the disease process has been anything but typical, if there is such an entity in mitochondrial disease. The limitation of syndrome nosology based on phenotypic hooks is considered, along with the progressive recognition of the unruly nature of biologic phenomena underlying disease, defeating our attempts to impose order by creating neat pigeon-holes based on perceived morphologic patterns with little or no knowledge of basic biology. While this conundrum can be seen with most genetic disorders, to one degree or another, the case of mitochondrial diseases offers the unique perspective that allows us to understand the limits of precision in prognostication, and indeed even in disease definition.

Also presented is a parent's perspective of the search for clear answers and the personal conclusion this family came to, that uncertainty should be taken as reason for hope.