“Is it Really Mito”

When an alternative Diagnosis should be considered

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Disclaimer

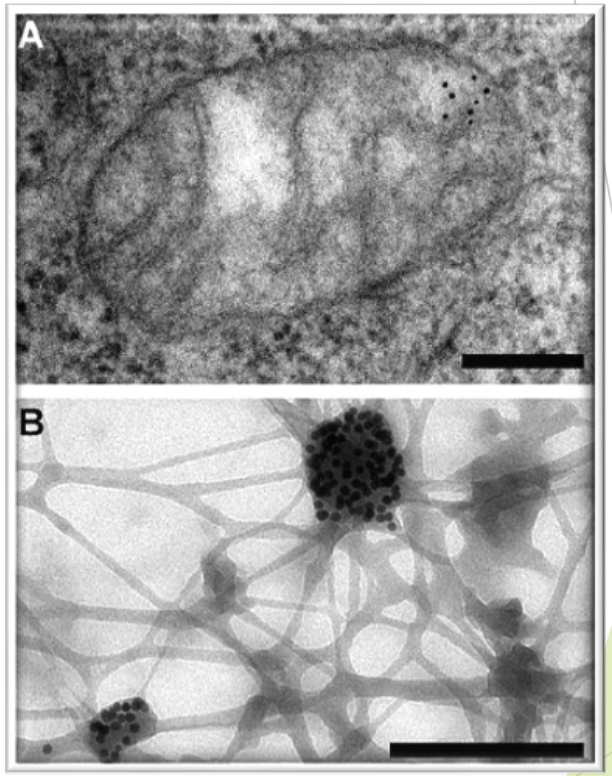
Dr Kendall and VMP Genetics have no financial interest in any laboratory.

OBJECTIVE

To review the approach to mitochondrial disease diagnosis, clinical red flags that suggest a non-mito diagnosis should be considered, why an alternative diagnosis should be entertained, and the tools utilized to reanalyze patients classified as mito.

Mitochondrial Energy Disorders

- ✓ Found in 1 in 4,000 individuals
- ✓ Carrier rate of common mtDNA mutations may be as high as 1 in 200
- ✓ Caused by an alteration in our inherited blueprint (gene mutation) or “toxic” affect of external factor such as medication
- ✓ Results in decreased energy production and localized or widespread problems



Common Problems In Mito

- ✓ Central Nervous system (Brain) problems such as developmental delays including AUTISM AND AUTISTIC FEATURES, loss of function, seizures, hypotonia, weakness, muscle pain, ptosis and CPEO, hearing loss
- ✓ Failure to thrive, short stature
- ✓ Chronic fatigue
- ✓ Gastrointestinal issues such as gastroparesis, chronic constipation and dysmotility and liver failure
- ✓ Autonomic dysfunction such as irregular heart rate and blood pressure and temperature instability with heat intolerance
- ✓ Endocrine problems such as diabetes or hypothyroidism
- ✓ Cardiomyopathy and heart rhythm abnormalities

How to Diagnose Mitochondrial disease

- ✓ Several tiers of testing are utilized to diagnose mitochondrial disease
- ✓ Constellation of clinical features
- ✓ Biomarker studies – lactate and pyruvate levels, CSF lactate, CPK, urine organic acids, carnitine levels.
- ✓ Radiographic studies – identification of mito related imagining abnormalities.
- ✓ Functional testing – examining the OXPHOS energy pathway.
- ✓ Gene testing – evaluation of mtDNA and nuclear mitochondrial genes
- ✓ Utilization of published Criteria such as the Bernier Criteria

Before Embarking on a Evaluation…

Make sure that you screen for other disorders like….

- ✓ Chromosome abnormalities
- ✓ Other inborn errors of metabolism
- ✓ Any other disorders that could explain the clinical presentation

Clinical "Red Flags"

- ✓ Predominately a seizure disorder
- ✓ Developmental delay syndrome, particularly with dysmorphic features, without multisystem involvement
- ✓ Isolated myopathy
- ✓ Static disease process
- ✓ No biochemical abnormalities
- ✓ "Gut" feeling of practitioner

Seizure Disorder Syndrome

- ✓ Patient presented at 6 months of age with infantile spasms
- ✓ Chromosomes, lysosomal enzymes, biotinidase assay, metabolic studies, all negative EXCEPT for a mildly increased lactate on one occasion
- ✓ Brain MRI, CSF testing negative; muscle biopsy complex I defect
- ✓ Clinical course notable for predominant seizure disorder and delays with no other system involvement
- ✓ All follow-up metabolic studies consistently negative
- ✓ Patient identified to have an SCN2A de novo gene mutation

Neurodevelopmental Gene Syndrome

- ✓ Patient presented at 12 months of age with hypotonia, DD and elevated lactate level
- ✓ Chromosome studies, telomeric FISH studies, metabolic studies, CSF testing all negative EXCEPT for a lactate of 14 with nL up to 12
- ✓ Muscle biopsy notable for complex I and IV defects
- ✓ Clinical course notable for static encephalopathy with no other system involvement and dysmorphic features
- ✓ Follow-up metabolic studies negative
- ✓ Patient identified to have de novo mutation in the ZEB2 gene associated with Mowat-Wilson Syndrome

Myopathy

- ✓ Patient presented at 6 years of age with congenital axial and proximal muscle weakness with several mildy increased CPK levels
- ✓ Metabolic studies unremarkable
- ✓ Muscle biopsy notable for histological changes consistent with a chronic myopathy and a complex I defect
- ✓ Clinical course notable for chronic, stable myopathy affected core and extremities without other system involvement
- ✓ Follow-up metabolic labs consistently normal
- ✓ Patient identified to have a de novo mutation in the COL6A2 gene associated with the Ullrich/Bethlem muscular dystrophy spectrum of disorders

EVEN IF IT REALLY LOOKS LIKE MITO…

- ✓ Patient presented at 4 years of age with ataxia and subsequently developed seizures and developmental delays.
- ✓ EMG and initial brain MRI were normal; ataxia studies for Freidrich's ataxia and ataxia telangiectasia were normal
- ✓ Muscle biopsy noted complex I defect; all other biochemical studies were negative.
- ✓ Follow-up brain MRI at age 7 years noted cerebellar atrophy
- ✓ Follow-up metabolic studies were negative
- ✓ Patient identified to have an autosomal recessive form of spastic ataxia, affecting the SACS gene

Implications of the CORRECT Diagnosis

- ✓ Allows for implementation of appropriate treatment modalities
- ✓ Prevents unnecessary interventions and testing
- ✓ Provides eligibility for clinical treatment trials, if available
- ✓ Provides accurate prognostic information
- ✓ Allows for accurate recurrence risks for subsequent pregnancies and other family members

Diagnostic Tools

- ✓ Genomic studies
  - *careful - "whole" does not mean 100%*
- ✓ Biochemical tissue assays
- ✓ Metabolic studies

Who Arrives at the Diagnosis?

- ✓ Labs do not diagnose patients, clinicians do
- ✓ Clinical acumen/experience of the doctor matters

We are not all the same!

Thank You!

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