Mitochondrial Diseases with Prominent Movement Disorders in Children

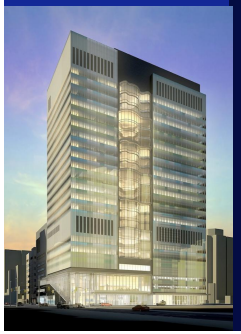
Ingrid Tein MD

Director, Neurometabolic Clinic and Research Laboratory

Division of Neurology

The Hospital for Sick Children

University of Toronto, Toronto, Canada



Disclosures

Canadian Institutes of Health Research

Canadian Foundation of Innovation

United Mitochondrial Diseases Foundation

Physicians' Services Incorporated Foundation

Heart and Stroke Foundation

Rare Diseases Foundation

Myositis Association

Foundation for Prader Willi Research

Mito2i Innovation Grant, University of Toronto

Learning Objectives

1. To identify phenotypes and genotypes of mitochondrial disorders with prominent movement disorders
2. To understand the modes of inheritance
3. To recognize potentially treatable vitamin/cofactor responsive mitochondrial movement disorders

Key messages

1. Movement disorders, such as dystonia, chorea, ataxia or myoclonus, alone or in combination with encephalopathy, seizures, stroke-like episodes, limb girdle weakness and neuropathy may be a prominent feature in a number of childhood mitochondrial disorders.

2. Dystonia, chorea and ataxia are important manifestations of Leigh syndrome which may arise from genes affecting mitochondrial function, in both mitochondrial (14 genes) and nuclear genomes (> 80 genes), most often involving Complexes I and/or IV of the respiratory chain.

3. Potentially treatable etiologies include thiamine-responsive pyruvate dehydrogenase deficiency, biotinidase deficiency which responds to biotin, and the biotin-thiamine responsive basal ganglia disease due to mutations in SLC19A3 which responds to biotin and thiamine.

Key messages

4. There are numerous mitochondrial disorders with ataxia including NARP (neuropathy, ataxia and retinitis pigmentosa) syndrome arising from heteroplasmic pathogenic variants in mtDNA and those due to nuclear-encoded POLG mutations which may present with MEMSA and ataxia neuropathy spectrum (MIRAS, SANDO).

5. Very important to identify are nuclear-encoded CoQ10 biosynthesis defects which may present with progressive cerebellar atrophy and ataxia and low muscle CoQ10 and which respond to high dose CoQ10 therapy.

6. MERFF (myoclonus, epilepsy and ragged red fibres) is a multisystem disorder characterized by myoclonus, often the first symptom, and can occur from childhood due to mtDNA mutations.

References

Cohen BH, Chinnery PF, Copeland WC. POLG-Related disorders. 2010 [updated 2018] In:Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, Amemiya A, editors. GeneReviews [Internet].Seattle (WA) University of Washington, Seattle; 1993-2021 Review

DiMauro S, Schon EA, Carelli V, Hirano M. The clinical maze of mitochondrial neurology. Nat Rev Neurol 2013; 9:429-444

Emmanuele V, Lopez LC, Berardo A, Naini A, Tadesse S, Wen B, D'Agostino E, Solomon M, DiMauro S, Quinzii C, Hirano M. Heterogeneity of coenzyme Q10 deficiency: patient study and literature review. Arch Neurol 2012; 69:978-83

Hirano M, Emmanuele V, Quinzii C. Emerging therapies for mitochondrial diseases. Essays Biochem 2018;62:467-481

Rahman S. Mitochondrial disease in children. J Intern Med 2020; 287:609-633 Review

Rahman J, Rahman S. Mitochondrial medicine in the omics era. Lancet. 2018 Jun 23;391(10139):2560-2574. doi: 10.1016/S0140-6736(18)30727-X. Epub 2018 Jun 18. PMID: 29903433 Review.

Rahman S, Thorburn D. Nuclear gene-encoded Leigh syndrome spectrum overview. 2015 [updated 2020] In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, Amemiya A, editors. GeneReviews [Internet].Seattle (WA) University of Washington, Seattle; 1993-2021 Review

Tabarki B, Al-Hashem A, Alfadhel M. Biotin-Thiamine-Responsive Basal Ganglia Disease. 2013 [updated 2020] In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, Amemiya A, editors. GeneReviews [Internet].Seattle (WA) University of Washington, Seattle; 1993-2021 Review

Thorburn DR, Rahman J, Rahman S. Mitochondrial DNA-associated Leigh syndrome and NARP. 2003 [updated 2017] In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, Amemiya A, editors. GeneReviews [Internet].Seattle (WA) University of Washington, Seattle; 1993-2021 Review