Mitochondrial neurological diseases: A clinician’s perspective

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Mitochondrial neurological disorders remain esoteric but fascinating to the clinician. Aspects of their biology illuminate the complexities of their clinical manifestations. The hallmark multiple organ dysfunction is traceable to failure of mitochondria, the ubiquitous organelles of energy generation. High energy cell populations that are post-mitotic and non-dividing at birth, are especially vulnerable as exemplified by the brain, retina, optic nerves, organ of Corti, skeletal and cardiac muscle, cardiac conduction system, renal tubular cells, endocrine and pancreatic exocrine glands. The accumulation of mutant mitochondria in vulnerable tissues may cause progressive worsening organ function. Similar mitochondrial segregation may increase abnormal cells in some tissues and decrease in others, shifting clinical dysfunction, say from bone marrow failure to myopathy. Cytoplasmic maternal inheritance is another distinctive feature: mitochondrial gene mutations are transmitted exclusively by the mother through the cytoplasm of the egg, to offsprings of both sexes. As the mutant mitochondria multiply and segregate randomly into different cell lines in the dividing egg, they reach different organs randomly accounting for diversity and variability of the phenotype among patients with the same mutation (mitotic heteroplasmy).

Some of the best defined syndromes due to mitochondrial gene defects are: Leber’s hereditary optic neuropathy (LHON); Kearns–Sayre syndrome (KSS) of chronic progressive external ophthalmoplegia, retinitis pigmentosa, sensory-neural deafness and cardiac conduction disturbances; chronic progressive external ophthalmoplegia (CPEO); the syndrome of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS); myoclonic epilepsy with ragged red fibers (MERRF); neuropathy with ataxia and retinitis pigmentosa (NARP/Leigh’s) and the recently identified LHON with dystonia and sporadic focal dystonia.

A paradigm shift occurred when the nuclear genome was found to regulate most of the mitochondrial biology including assembly, replication and maintenance and autosomally transmitted mutations in the nuclear genome were felt to cause many mitochondrial syndromes. Their phenotypes are often similar to maternally inherited KSS, CPEO and Leigh’s syndrome except that they are more homogeneous. An example of nuclear syndrome is myoneural gastrointestinal encephalopathy (MNGIE) due to thymidine pyrophosphorylase gene mutation, characterized by CPEO, dementia, leukodystrophy and intestinal dysmotility.

Dysfunction of the brain, retina, hearing, extracocular and other skeletal muscle with hints of other organ impairments form the core clinical picture. Although constellations such as CPEO, KSS and LHON are readily recognizable, many patients show only fragments of such entities and presentations may straddle different syndromes. Moreover, first presentations may appear in late adulthood, organ dysfunction may shift form one to another, and characteristic maternal inheritance can be masked by the phenotypic variability and not all syndromes have yet been described. Thus, mitochondrial disorders enter into the differential diagnosis of many common as well as rare neurological symptoms. Recurrent acute optic neuritis, seizures, especially myoclonic, stroke and TIA and migraine-associated neurological symptoms, episodic ataxia, exercise-induced fatigue, sometimes with myoglobinuria and episodic encephalopathy and coma may be the leading symptoms. Provocation of the episodes by infection, dehydration, fasting or surgery is characteristic. Unexplained syndromes of progressive dementia and psychosis, complex movement disorders resembling Wilson’s disease or multiple system atrophy or spinocerebellar ataxias and progressive blindness and deafness should raise the suspicion of mitochondrial disease. Rare cases present as chronic fatigue and polymyalgia rheumatica. Axonal or CIDP-like neuropathy, autonomic neuropathy indicated by anhidrosis and gastrointestinal dysmotility manifest as anorexia, nausea, diarrhea, abdominal pain and pseudo-intestinal obstruction are common.

Considering the mitochondrial disorders while evaluating puzzling neurological symptoms is the key diagnostic step.
External ophthalmopresis, myopathy, pigmented retinopathy, optic atrophy, sensory neural deafness should be sought. Diagnosis is supported by short stature, mental and other developmental delays, symmetrical lipomatosis, cardiac conduction system abnormalities and endocrinopathies such as diabetes and rarer hypoparathyroidism, hypoadrenalism, hypogonadism. Scrutiny of the family by history and examination for even minor expression of the disease is helpful.

Laboratory tests done in the usual evaluation of presenting symptoms may suggest the diagnosis: MRI for stroke showing infarct-like lesions crossing major arterial zones, lactic acid peaks by proton MR spectroscopy and lesions that remit and relapse are typical for MELAS. In cases with widespread brainstem dysfunction and ataxia, bilateral extensive T-2 hyperintensities in the brainstem and basal ganglia typify Leigh’s disease. Basal ganglia calcifications and subcortical leukoencephalopathy are seen in MNGIE and MELAS.

Specialised tests guided by the clinical picture provide supportive evidence but may not be pathognomonic and may be abnormal in other conditions. Elevated serum lactic acid (≥ 2.2 mmols/L) is a key finding. Blood sample is obtained after tourniquet is released to avoid spurious results and repeated if initially normal when clinical suspicion is strong. Serum pyruvate is helpful when lactate is high as the lactate/pyruvate ratio is typically in the range of 50:1 to 250:1 compared to normal of < 25:1. CSF lactate is a good and stable marker for MELAS and other encephalomyopathies. Evaluation of muscle biopsy is an excellent, standardised tool with or without clinical myopathy, amenable to histological, genetic and biochemical analysis. Abundant ragged red fibers, representing clusters of mitochondria, on modified Gomori stain, provide strong support for both mitochondrial and nuclear gene defects. Cytochrome c oxidase (COX) stain reveals COX negative fibers seen in some mitochondrial gene lesions. Electron microscopy may detect morphologically distorted mitochondria. Activity of the respiratory chain enzymes in frozen samples are not routinely needed.

Genetic tests in sophisticated molecular laboratories can identify mutations in many syndromes of mitochondrial genes but in only a few of the nuclear genes. Search can be focused for some syndromes: mitochondrial mutations of t-RNA for MELAS and MERRF, protein coding genes of NARP, LHON and KSS can be detected in lymphocytes. Muscle is tested for the single deletions of sporadic CPEO. A battery of tests is needed in cases without distinctive syndrome. Mutation of thymidine phosphorylase gene causing MNGIE is an example of nuclear gene defect.

Early recognition of the common cardiac conduction disturbance and preventive pacemaking are important and life-saving. Valproate for seizures is best avoided for fear of hepatotoxicity. Disease modifying treatment is in its infancy and evidence of efficacy is meager, short-term and conflicting. A cocktail of substances known to physiologically modulate the mitochondria or act as antioxidants, is commonly prescribed hoping to bolster the failing organelles and bring clinical benefit. Cofactors such as coenzyme Q10, levo-carnitine, thiamine, riboflavin, vitamin E, folate, lipic acid and selenium are the usual ingredients. Rapid advances in genetic engineering to correct these disorders raise hope but likely to take a few decades.

Discovery of the significant role of mitochondrial dysfunction in the pathogenesis of Parkinson’s, Alzheimer’s, motor neuron and Wilson’s diseases and the identification of frataxin of Friedreich’s ataxia and spastin of hereditary spastic paraplegia as integral to mitochondria, are bringing together many threads in the mitochondrial neurology story with potential beneficial spin offs for patients with these syndromes, inherited or acquired.

References

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