Neuropsychiatric Features in Primary Mitochondrial Disease

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KEYWORDS

• Mitochondrial • Neuropsychiatric • Behavioral • Autism • Depression • Anxiety • Bipolar disorder • Schizophrenia

KEY POINTS

- There is some evidence to suggest that mitochondrial dysfunction plays a role in neuropsychiatric illness; however, the data are inconclusive.
- Onset of psychiatric illness often proceeds onset of mitochondrial disease symptoms.
- Many classic mitochondrial syndromes are associated with psychiatric illness.
- Children and adults have co-morbid mitochondrial disease and psychiairic illness.

INTRODUCTION

Mitochondrial diseases are a clinically heterogeneous group of disorders that ultimately result from dysfunction of the mitochondrial respiratory chain. The respiratory chain (also known as the electron transport chain) is a series of 5 protean complexes

Disclosure Statement: S.E. Marin has received funding as part of a mitochondrial fellowship from the National Institutes of Health (NIH 2U54NS078059-04). She is involved in the North American Mitochondrial Disease Consortium (NAMDC). She has been a nonpaid member of pharmaceutical company sponsored clinical studies, including those sponsored by Edison Pharmaceuticals, Raptor Pharmaceuticals, and Stealth Peptides. R.P. Saneto has received grant funding to perform clinical studies on mitochondrial diseases from National Institutes of Health (NIH 2U54NS078059-04) and Edison Pharmaceuticals. He is a nonpaid member of the DSMB board for REATA Pharmaceuticals 408-C-1402 and 408-C-1403.

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Neurol Clin 34 (2016) 247–294
http://dx.doi.org/10.1016/j.ncl.2015.08.011 **neurologic.theclinics.com**
0733-8619/16/$ – see front matter

that are linked together to reduce molecular oxygen to water (oxidation) and phosphorylate adenosine diphophosphate to adenosine triphosphate (ATP).[1] The active shuttling of electrons begins when complex I (nicotinamide adenine dinucleotide with hydrogen [NADH] dehydrogenase or NADH:ubiquinone oxidoreductase) accepts electrons from NADH produced in the Krebs cycle and passes them to coenzyme Q10 (ubiquinone). Ubiquinone also receives electrons from reduced flavin adenine dinucleotide ($FADH_2$) via complex II (succinate dehydrogenase: SDH). Electrons are then shuttled from ubiquinone to complex III (cytochrome bc_1 complex) and then to complex IV (cytochrome c oxidase: COX), which reduces molecular oxygen to water. An electrochemical gradient is produced as protons are pumped to the intermembrane space between the inner and outer mitochondrial membrane as electrons shuttle between complexes I to IV. Using this proton gradient, complex V (ATP synthase) acts as an ion channel allowing for proton flux back into the mitochondrial matrix, resulting in the release of free energy, which drives ATP synthesis (**Fig. 1**).

The mitochondria are considered the "power plants" of the cell; the majority of cellular energy is in the form of ATP. The proteins required for mitochondrial structure and function are derived from both nuclear DNA (nDNA) and mitochondrial DNA (mtDNA) encoded genes.[2] Unlike nDNA, which exists as a single copy within the nucleus of each cell, the mtDNA exists as multiple copies within the mitochondria of each cell. Human mtDNA is a circular, double-stranded molecule containing approximately 16,569 base pairs and encodes for 37 genes: 22 transfer ribonucleic acids (tRNAs), 2 ribosomal RNAs (rRNAs), and 13 polypeptides that are incorporated into the electron transport chain subunits I, III, IV, and V (see **Fig. 1**).[3,4] These 13 polypeptides are important for efficient generation of ATP, but represent a small fraction of the total number of respiratory chain subunits, the remainder of which are encoded by nDNA.

The dependence on both nuclear and mitochondrial gene products, combined with the unique physiology of mitochondrial function, can create a wide range of disease expression. Mitochondrial disorders owing to mtDNA-encoded mutations differ from those secondary to nDNA mutations in various ways. Inheritance of mtDNA is through the maternal lineage rather than following classic Mendelian genetics. However, because mitochondrial disease may be secondary to nuclear-encoded mutations, absence of maternal inheritance does not rule out the possibility of an underlying mitochondrial disease. Second, unique mitochondrial physiology can alter disease expression. Every cell contains hundreds to thousands of mtDNA molecules. When mutations arise, a mixture of wild-type and mutant mtDNA (heteroplasmy) can exist that are then randomly distributed to daughter cells through mitotic segregation. This random segregation of normal and mutant mtDNA results in different mutation loads in various tissues (see **Fig. 1**).[5,6] When the mutation load reaches a certain "threshold," features of mitochondrial dysfunction in that tissue become apparent.[7] The percentage level of mutant mtDNA may vary among individuals within the same family, and also among organs and tissues within the same individual.[8] The energetic requirement between organs varies and, therefore, expression of organ dysfunction can vary within the individual. Additionally, the mtDNA is susceptible to a higher mutation and base pair substitution rate compared with nDNA owing to the lack of histones and DNA repair mechanisms and has been considered by some as the "weak point" of the human genome.[9] A high level of polymorphisms in mtDNA have been reported, some of which have been linked to susceptibility to certain diseases.[10]

The understanding of mitochondrial disorders is in its youth, with the first pathogenic mutation identified fewer than 30 years ago.[11] Mitochondrial disorders were previously