Review
Journal of Epilepsy Research
pISSN 2233-6249 / eISSN 2233-6257

Mitochondrial Diseases

Young-Mock Lee, MD, PhD

Department of Pediatrics, Gangnam Severance Hospital and Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Korea

Received November 17, 2011
Accepted December 13, 2011

Corresponding author: Young-Mock Lee
Department of Pediatrics, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 135-720, Korea
Tel. +82-2-2019-3354
Fax. +82-2-3461-9473
E-mail; ymleemd@yuhs.ac

Mitochondria contain the respiratory chain enzyme complexes that carry out oxidative phosphorylation and produce the main part of cellular energy in the form of ATP. Although several proteins related with signalling, assembling, transporting, and enzymatic function can be impaired in mitochondrial diseases, most frequently the activity of the respiratory chain protein complexes is primarily or secondarily affected, leading to impaired oxygen utilization and reduced energy production. Mitochondrial diseases usually show a chronic, slowly progressive course and present with multiorgan involvement with varying onset between birth and late adulthood. Neuromuscular system is frequently affected in mitochondrial diseases. Although there is actually no specific therapy and cure for mitochondrial diseases, the understanding of the pathophysiology may further facilitate the diagnostic approach and open perspectives to future in mitochondrial diseases. **(2012;2:1-4)**

Key words: Mitochondria; Mitochondrial disease; Respiratory chain complex; Energy metabolism

Introduction

In 1962, Luft, *et al.* made a suggestion of mitochondria as an intracellular organelle related to human diseases. They supported the idea with evidence of mitochondrial function abnormality observed in a hypermetabolic patient. Later reports also showed respiratory chain dysfunctions in patients with encephalomyopathy confirming the role of mitochondria in human diseases.[1-3] Though sometimes the concept of mitochondrial disease is being used to indicate abnormal metabolic pathways within mitochondria, it generally implies an energy metabolic disease caused by abnormal respiratory chain reaction which is followed by decreased energy production with various clinical symptoms as a result. Recently, mitochondria is drawing further attention as its role in the aging process and common chronic illness such as chronic heart failure, diabetes mellitus, and neurodegenative diseases become known more and more.[4-6]

Oxidative phosphorylation and genetics

Mitochondrial respiratory chain consist of 5 enzyme complexes including more than 100 different protein units that are needed for oxydative phosphorylation and ATP production.[7] Mitochondrial DNA (mitochondrial DNA, mtDNA) encode for each unit of 4 enzyme complexes among total of 5. It codes for 7 units of complex I (NADH dehydrogenase), 1 of complex III (cytochrome c reductase), 3 of complex IV (cytochrome c oxidase), and 2 of complex V (ATP synthase). Complex II (succinate dehydrogenase) is encoded by nuclear DNA. Respiratory chain reaction produces ATP through oxydative phosphorylation using proton concentration difference in the inner membrane of mitochondria.[4]

Oxydative phosphorylation is precisely controlled adjusting to different physiologic circumstances. Damage to the ability of oxydative phosphrylation caused by nuclear DNA or mitochondrial DNA (mtDNA) mutations result in different types of mitochondrial diseases. Therefore, diverse types of inheritance occur depending on the cause of the original mutation.[4-8]

Two types of mutation are considered significant in mtDNA mutation. Point mutations and rearrangement that includes deletion and duplication are the ones. If the mutation takes place during embryonic cell period, it follows maternal inheritance. Mutations can also happen in somatic cells making a sporadic occurrence of disease. If the amount of normal mtDNA is enough to compensate the defect in a cell with heteroplasmy, that is coexisting state of mutated and normal mtDNA, the damage in respiratory chain reaction can be prevented. However, when the ratio between normal

and mutated mtDNA is shifted more than certain level, dysfunction of respiratory chain reaction occurs. The threshold level to induce the dysfunction depends on the amount of energy required in a certain tissue. Central nervous system, heart, muscle, liver, and kidneys are relatively more prone to manifest clinical symptoms due to their higher energy requirement. The rate of heteroplasmy does not stay consistent during cell division. The inequable distribution of mtDNA occurs during embryonic period can induce unevenness in the proportion of mutated and normal mtDNA among different tissues in the same individual or among cells within the same tissue.[7,9,10] Also, clinical symptoms induced by specific mtDNA manifest at a very wide spectrum of severity due to the diversity of mutated mtDNA proportion that occur during meiosis and somatic cell division and due to the tissue-specific differences of energy requirement as well.

However, subunits of respiratory chain complex are determined much more by nuclear DNA than by mtDNA. There have been several types of nuclear DNA mutation identified till now. In those cases, they follow Mendel's law of inheritance with varying phenotypes and not that of maternal inheritance.[8,9]

Clinical characteristics and specific mitochondrial diseases

Mitochondrial diseases can develop at different stages of life-from early embryonic period to adulthood. One of the most important characteristics of mitochondrial disease is the wide variety of clinical symptoms that originate from either single or multiple organs. This diversity comes from degree of heteroplasmy, types of mutations, difference in the threshold value of each tissue for biochemical manifestations, and coordination effect between nuclear and mitochondrial genes.[11,12]

There is no particular clinical feature that can describe mitochondrial disease. Most patients complain a combination of several symptoms originating from different organs such as brain, nerve, muscle, endocrine glands, heart, eye, ear, intestine, kidney, and bone marrow, etc. developing at different times. Tissues or organs such as muscle, brain, heart, liver, etc. that require more oxygen and energy tend to be affected first. Naturally, the most common symptoms found in mitochondrial disease are neuromuscular related ones. When atypical symptoms appear in relatively common disease involving several organs, one can suspect mitochondrial disease.[12-14]

Syndromes such as MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes), MERRF (myoclonus epilepsy and ragged-red fibers), and Kearns-Sayre syndrome (retinitis pigmentosa, progressive external ophthalmoplegia, ataxia and heart conduction defects) represent mitochondrial diseases.[14-19]

MELAS and MERRF syndrome develop because of the mutation of tRNA gene while Kearns-Sayre syndrome develop from large deletion of mtDNA genes.[17,18] Interestingly, clinical symptoms can be quite variable even when related with specific mutation. For example, A3243G mutation of $tRNA^{Leu\ (UUR)}$ gene is related with progressive external ophthalmoplegia, diabetes mellitus, and MELAS. The reason for variable manifestations are not fully understood yet. The distribution of mtDNA mutations and their interactions with other nuclear genes are thought to play an important role, though.

Pediatric patients usually share mtDNA deletion in many different tissues and suffer serious symptoms from various system dysfunctions such as anemia, pancreas failure, nephropathy, hepatic failure, diabetes mellitus, or other endocrinologic abnormalities. Ptosis, oculomotor dysfunction, progressive paralysis of extraocular muscle accompanying musculoskeletal weakness indicate Kearns-Sayre syndrome.[15,16]

Leber's hereditary optic neuropathy (LHON) is a genetic disease with maternal inheritance that causes blindness in young adults. Over 90% of its patients show different point mutations in mtDNA that are responsible for complex I structure.[14,19]

Point mutation in genes that code ATP synthase units cause neurogenic myopathy, ataxia, retinitis pigmentosa (NARP), and Leigh syndrome. High degree of mtDNA mutation results in Leigh syndrome which appear in pediatric age while low degree of the mutation causes NARP syndrome which is less severe and appear at a later stage of life.[20]

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) syndrome is characterized by decrease in enzyme activities of mitochondrial respiratory chain and other abnormalities of mtDNA.[21] It is known to be related with mutations of thymidine phosphorylase gene that codes nuclear DNA. Some say that the inactive thymidine phosphorylase changes cellular thymidine pools necessary to maintain mtDNA and that might be responsible for the pathophysiology of MNGIE syndrome.

Diagnosis and treatment of mitochondrial diseases

Diagnostic approach should include patient and family history,

serological examination, and neurological workup as in diagnosing other diseases and specific biochemical studies, muscle biopsy, and molecular genetic studies as well.[22,23]

The most useful basic test is to check serum lactate level. In cases when pyruvate oxidation in mitochondria is disturbed due to abnormalities in Pyruvate dehydrogenase complex (PDHC), Krebs cycle or electron transmission, excessive pyruvate can be either transformed into alanine or reduced to lactate resulting in increase of their blood level. The lactate:pyruvate ratio can be either maintained or increased depending on the degree of oxidation-reduction in tissue. Since the increase of serum lactate level can be equivocal in patients with mitochonrial encephalopathy, it is helpful to collect samples from cerebrospinal fluid.[24,25]

There are some characteristic features of brain MRI that are occasionally observed in mitochondrial disease patients.[26] In Leigh syndrome, one can see bilateral high signal lesions in basal ganglia and brain stem while in MELAS stroke-like lesions are seen usually in posterior parts of the brain, especially in occipital lobe. Abnormal densities can be observed in central white matter in Kearns-Sayre syndrome and calcification of basal ganglia in cases of Kearns-Sayre syndrome and MELAS. Confirmation of lactate peak in Magnetic resonance spectroscopy can be useful in making diagnosis.[27]

In most cases, diagnostic approaches to mitochondrial diseases include biochemical assays that measure activities of enzymes in respiratory chain reaction, morphological observation using microscopic tools, and molecular genetic studies to examine mtDNA or nuclear DNA mutation.

Though there have been a great improvement in understanding the pathophysiology of mitochondrial disease, no definitely effective mode of treatment has been established yet.[28,29] Coenzyme Q is reported to show two functions as an electron carrier in mitochondrial respiratory chain reaction and as well as a scavenger molecule. Riboflavin, tocopherol (vitamin E), succinate, ascorbate (vitamin C), menadione, and nicotinamide have also been used to treat mitochondrial disease with deficiency of specific enzyme. Peptide nucleic acids therapy and satellite cell activation therapy are also in trial. However, gene therapy on defective gene itself is thought as the ultimate way of treating the disease after all. [30-33]

Conclusions

Mitochondrial disease is known to be rare. But this might just be due to diagnostic difficulties and the disease might be more common in reality. As the importance of diagnosing mitochondrial disease is widely accepted and many studies in various fields using different kinds of method are in progress, we believe that there will come a day when those efforts bear fruits not only in enabling a precise diagnosis but also in improving its treatment.

References

1. Nass MMK, Nass S. Intramitochondrial fibers with DNA characteristics. I. Fixation and electron staining reactions. *J Cell Biol* 1963;19:593-611.
2. Anderson S, Bankier AT, Barell BG, et al. Sequence and organization of the human mitochondrial genome. *Nature* 1981;290:457-65.
3. Bibb MJ, Van Etten RA, Wright CT, et al. Sequence and organization of mouse mitochondrial DNA. *Cell* 1981;26:167-80.
4. McFarland R, Taylor RW, Turnbull DM. Mitochondrial disease-its impact, etiology and pathology. *Curr Top Dev Biol* 2007;77:113-46.
5. Wallace DC. Mitochondrial genetics: a paradigm for aging and degenerative diseases? *Science* 1992;256:628-32.
6. Luft R. The development of mitochondrial medicine. *Proc Natl Acad Sci USA* 1994;91:8731-8.
7. Lightowlers RN, Chinnery PF, Turnbull DM, et al. Mammalian mitochondrial genetics: heredity, heteroplasmy and disease. *Trends Genet* 1997;13:450-5.
8. Chan DC. Mitochondria: dynamic organelles in disease, aging and development. *Cell* 2006;125:1241-52.
9. Haas RH, Parikh S, Falk MJ, et al. The in depth evaluation of suspected mitochondrial disease. *Mol Genet Metab* 2008;94:16-37.
10. Thorburn DR, Sugiana C, Salemi R, et al. Biochemical and molecular diagnosis of mitochondrial respiratory chain disorders. *Biochem Biophys Acta* 2004;1659:121-8.
11. Holt IJ, Harding AE, Morgan-Hughes JA. Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies. *Nature* 1988;331:717-9.
12. Scaglia F, Towbin JA, Craigen WJ, et al. Clinical spectrum, morbidity and mortality in 113 pediatric patients with mitochondrial disease. *Pediatrics* 2004;114:925-31.
13. Jackson MJ, Shaefer JA, Johnson MA, Morris AA, Turnbull DM, Bindoff LA. Presentation and clinical investigation of mitochondrial respiratory chain disease. A study of 51 patients. *Brain* 1995;118:339-57.
14. Chinnery PF, DiMauro S, Shanke S, et al. Risk of developing a mitochondrial DNA deletion disorder. *Lancet* 2004;364:592-6.
15. Zeviani M, Moraes CT, DiMauro S, et al. Deletions of mitochondrial DNA in Kearns-Sayre syndrome. *Neurology* 1988;38:1339-46.
16. Lestienne P, Ponsot G. Kearns-Sayre syndrome with muscle mitochondrial DNA deletion. *Lancet* 1988;1:85.
17. Goto YI, Nonaka I, Horai S. A mutation in the tRNALeu (UUR) gene

associated with the MELAS subgroup of mitochondrial encephalomyopathies. *Nature* 1990;348:651-3.
18. Shoffner JM, Lott MT, Lezza AMS, et al. Myoclonic epilepsy and ragged-red fiber disease (MERRF) is associated with a mitochondrial DNA tRNALys mutation. *Cell* 1990;61:931-7.
19. Nikoskelainen EK, Savontaus M-L, Wanne OP, et al. Leber's hereditary optic neuroretinopathy, a maternally inherited disease. *Arch Ophthalmol* 1987;105:665-71.
20. Shoffner JM, Wallace DC. Oxidative phosphorylation diseases and mitochondrial DNA mutations: diagnosis and treatment. *Annu Rev Nutr* 1994;14:535-68.
21. Morris AA, Appleton RE, Power B, et al. Guanidinoacetate methyltransferase deficiency masquerading as a mitochondrial encephalopathy. *J Inherit Metab Dis* 2007;30:100.
22. Wolf NI, Smeitink JAM. Mitochondrial disorders. A proposal for consensus diagnostic criteria in infants and children. *Neurology* 2002; 59:1402-5.
23. Morava E, van den Heuvel L, Hol F, et al. Mitochondrial disease criteria. Diagnostic applications in children. *Neurology* 2006;67: 1823-6.
24. Hutchesson A, Preece MA, Gray G, Green A. Measurement of lactate in cerebrospinal fluid in investigation of inherited metabolic disease. *Clin Chem* 1997;43:158-61.
25. Chow SL, Rooney ZJ, Cleary MA, Clayton PT, Leonard JV. The significance of elevated CSF lactate. *Arch Dis Child* 2005;90:1188-9.
26. Haas RH, Dietrich R. Neuroimaging of mitochondrial disorders. *Mitochondrion* 2004;4:471-90.
27. Jeppesen TD, Quistoriff B, Wibrand F, et al. 31P-MRS of skeletal muscle is not a sensitive diagnostic test for mitochondrial myopathy. *J Neurol* 2007;254:29-37.
28. Kaufmann P, Engelstad K, Wei P, et al. Dichloroacetate causes toxic neuropathy in MELAS. A randomized, controlled clinical trial. *Neurology* 2006;66:324-33.
29. Koga Y, Akita Y, Nishioka J, et al. L-arginine improves the symptoms of stroke like episodes in MELAS. *Neurology* 2005;64:710-2.
30. Taylor RW, Chinnery PF, Turnbull DM, et al. Selective inhibition of mutant human mitochondrial DNA replication in vitro by peptide nucleic acids. *Nat Genet* 1997;15:212-5.
31. Clark KM, Bindoff LA, Lightowlers RN, et al. Reversal of a mitochondrial DNA defect in human skeletal muscle. *Nat Genet* 1997;16:222-4.
32. Rotig A, Appelkvist EL, Geromel V, et al. Quinone-responsive multiple respiratory-chain dysfunction due to widespread coenzyme Q10 deficiency. *Lancet* 2000;356:391-5.
33. Bugiani M, Lamantea E, Invernizzi F, et al. Effects of riboflavin in children with complex II deficiency. *Brain Dev* 2006;28:576-81.