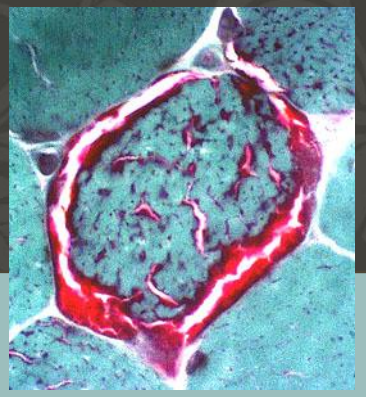
MYOCLONIC EPILEPSY WITH RAGGED RED FIBERS (MERRF)

By- Promie Faruque

PHYSIOLOGY



-MERRF is a rare panethnic mitochondrial disease which is caused by mutations in the mtDNA

-It mainly affects the muscle tissue and the nervous system

-Onset can range from childhood to adulthood, but typically symptoms show after a normal early development

-As one ages, symptoms start progressing

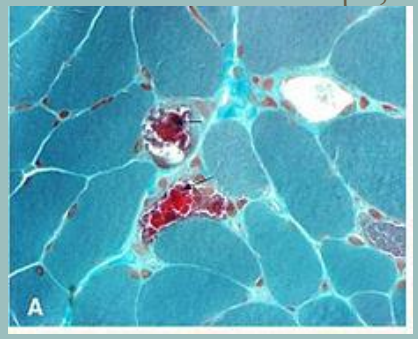
-Because MERRF is a heteroplasmic disease, phenotypes may vary from person to person

-Myoclonus is usually the first symptom

-It is later followed by epilepsy, ataxia, physical weakness, and dementia

-Other characteristics include difficulty speaking, short stature, hearing loss, peripheral neuropathy, and optic atrophy

-When muscle cells of an affected individual are stained and viewed under a microscope, the cells appear as ragged-red fibers making the cells abnormal



MOLECULAR CAUSE

-MERRF is a mitochondrial disease—meaning that its pathway is matrilineal

-It is caused by point mutations in the mtDNA

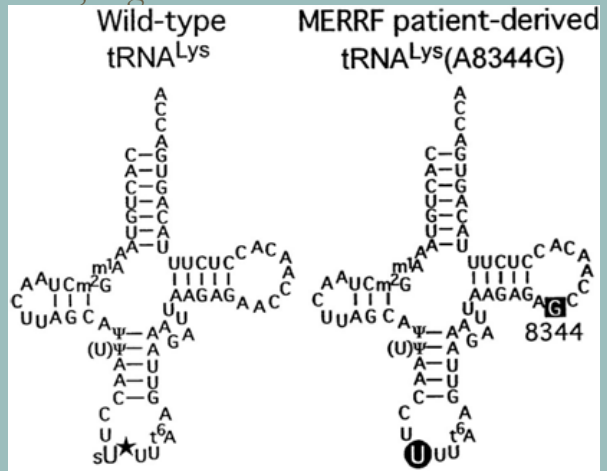
-Mutations typically occur in the MT-TK (Mitochondrially encoded tRNA lysine) , MT-TL1 (Mitochondrially encoded tRNA leucine 1), MT-TH (Mitochondrially encoded tRNA histidine), and MT-TS1 (Mitochondrially encoded tRNA serine 1) genes which are contained in mitochondrial DNA

-More than ninety percent of the patients have a point mutation on MT-TK gene which codes for $tRNA^{lys}$

-This is an A-to-G transition at nucleotide 8344

-The $tRNA^{lys}$ helps in the assembly of proteins for oxidative phosphorylation

-These mutations make the mitochondria incapable of using oxygen, producing energy, and making proteins—because there's a lack of energy production, organs and tissues that use a lot of energy, like the brain and the muscles, fail to function adequately



CURRENT TREATMENTS AND LIMITS

-Currently there is no cure and there are a few treatments available

-Treatments are symptomatic and palliative

-Prenatal testing can be done, but it won't give too much information

-Valproic Acid- Used to treat myoclonic epilepsy; causes secondary carnitine deficiency which can impair the functioning of the mitochondria; it is strongly advised to avoid using this, but if needed, to use it with L-Carnitine supplements

-Other treatments for myoclonic epilepsy include levetiracetam, clonazepam, and zonisamide

-Vitamin supplements that help optimize the activity of the OXPHOS complexes

-Coenzyme Q and L-Carnitine Supplements- Help to improve mitochondrial functioning

-Antiepileptic drugs are used to treat seizures

-Physical therapy and aerobic exercise are used to improve impaired motor ability

PROPOSED CURE AND LIMITS

-Over ninety percent of MERRF patients have a point mutation on the MT-TK gene, so cloning and inserting the MT-TK gene would be the most effective cure

-To do this, the wild-type MT-TK gene would be inserted into a plasmid, made into recombinant DNA, and then inserted into the patient

-When recombinant DNA has been inserted into the patient, the DNA can replicate and code for the wild type $tRNA^{lys}$ codon

-While the current treatments are mainly symptomatic and can only treat one manifestation of MERRF disease at a time, using a plasmid to deliver the insert of the MT-TK gene into the affected individual may be able to treat many of the manifestations of the disease

-Because of the heteroplasmic nature of the disease—inserting the wild type MT-TK into a patient can treat it efficiently since it will be able to treat it no matter what phenotype a patient exhibits

-However, one limitation to this is that in some rare circumstances, an individual may have more than one mutated gene, making it harder to treat the disease like this

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