Mitochondrial dysfunctions in Patients with Migraine

Thesis
Submitted for Partial Fulfillment of MSC Degree in Neuropsychiatry

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List of Abbreviations

ADP	**:**	Adenosine Diphosphate
ALS	**:**	Amyotrophic Lateral Sclerosis
ANAT	**:**	L-Aspartate *N*-Acetyltransferase
ATP	**:**	Adenosine Triphosphate
CACNA!A	**:**	Calcium Channel Alpha 1
CADASIL	**:**	Cerebral Autosomal Dominant Arteriopathy with Subcortical Leucoencephalopathy and Stroke
CCM	**:**	Choline Containing Metabolites
CEN	**:**	Central Executive Network
CGRP	**:**	Calcitonin Gene-Related Peptide
Cho	**:**	Choline
CNS	**:**	Central Nervous System
COA	**:**	Coenzyme A
COQ10	**:**	Coenzyme Q10
COX	**:**	Cytochrome C Oxidase
CSD	**:**	Cortical Spreading Depression
DMN	**:**	Default Mode Network
DNA	**:**	Double Stranded Deoxyribonucleic Acid
ETC	**:**	Electron Transport Chain.
18FDG-PET	**:**	18fluoro-2-Deoxy-D-Glucose Positron Emission Tomography Computed
FHM1	**:**	Familial Hemiplegic Migraine Type 1
fMRI	**:**	Functional Magnetic Resonance Imaging
GABA	**:**	Gamma-Aminobutyric Acid
Gln	**:**	Glutamine (Gln)
Glu	**:**	Glutamate (Glu)
GLX	**:**	Glutamine/Glutamate
HIS	**:**	Headache Classification Committee of the International Headache Society
hsCRP	**:**	High-Sensitivity CRP
5-HT	**:**	Serotonin
KCNK 18	:	Potassium Two Pore Domain Channel Subfamily K Member 18
LC-MS	**:**	Liquid-Chromatography– Mass Spectrometry

MA	**:**	Migraine With Aura
MAO	**:**	Monoamine-Oxidase
mDNA	**:**	Mitochondrial Double Stranded Deoxyribonucleic Acid
MELAS	**:**	Mitochondrial Myopathies, Lactic Acidosis and Stroke-Like Episodes
MERRF	**:**	Myoclonic Epilepsy With Ragged Red Fibers
MI	**:**	Myoinositol(MI)
MMPs	**:**	Matrix Metalloproteases
MRS	**:**	Magnetic Resonance Spectroscopy
1H-MRS	**:**	Proton Magnetic Resonance Spectroscopy
31P-MRS	**:**	31P-Magnetic Resonance Spectroscopy
MwoA	**:**	Migraine Without Aura
NAA	**:**	N-Acetyl-Aspartate.
NAAG	**:**	*N*-Acetylaspartylglutamate
NAALADase	**:**	*N*-Acetylated-A-Linked-Amino Dipeptidase
NADH	**:**	Nicotinamide Adenine Dinucleotide
NARP	**:**	Neurogenic Muscle Weakness, Ataxia, and Retinitis Pigmentosa
nDMA	**:**	Nuclear Double Stranded Deoxyribonucleic Acid
NGF	**:**	Nerve Growth Factor
NO	**:**	Nitric Oxide
NOS	**:**	Nitric Oxide Synthase
NTs	**:**	Neurotransmitters
PCR	**:**	Phosphocreatine
PDH	**:**	Pyruvate Dehydrogenase.
PRVEP	**:**	Pattern Visual Evoked Potential
rs-fMRI	**:**	Resting-State-Fmri
ROS	**:**	Reactive Oxygen Species
RRFs	**:**	Ragged Red Fibers
TCA	**:**	Tricarboxylic Acid
TRESK	:	TWIK-related spinal cord K(+) channel

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Introduction

INTRODUCTION

Migraine is a common, disabling, primary headache disorder, with episodic manifestations that affects women three times more than men **(Edmeads and Mackell 2002)**. Migraine is characterized by recurrent and often unilateral, vascular throbbing head pain and an additional symptoms which can include nausea, emesis, photophobia, phonophobia. Other symptoms may include visual and sensory disturbances **(Goadsby 2003).**

Migraine is a complex disorder caused by an interplay between predisposing genetic variants and environmental factors **(Stuart and Griffiths 2012).** According to classification criteria of the International Headache Society, migraine is sub-divided into two subtyps, namely migraine with aura (MA) and migraine without aura (MwoA) **(Headache Classification Committee of the International Headache Society {HIS} 2018).**

The pathophysiology is largely unknown despite intensive research and intense of interest because of the high prevalence and socioeconomic impact **(Edmeads and Mackell 2002).** Subcortical structures, mainly including brainstem, hypothalamus and thalamus, are involved in the generation of migraine attacks **(Goadsby 2009).** Neuronal hyperexcitability and trigemino-vascular activation are regarded to play an important role in migraine pathogensis **(Tsujikawa et al. 2014)**. The brainstem activates the trigemino-vascular system, which then stimulates perivascular trigeminal sensory afferent nerves with release of vasoactive neuropeptides, resulting in vasodilation and transduction of central nociceptive information **(Tepper et al. 2001).**

Other pathomechanism of migraine is cortical spreading depression (CSD) triggered by mitochondrial dysfunction resulting in calcium release to the cytosol, excessive production of reactive oxygen

species (ROS), and deficient oxidative phosphorylation with consecutive energy failure **(Yorns and Hardison 2013)**. The migraine attacks trigger oxidative stress. Oxidative stress elicits neurogenic inflammation via signals from the TRPA1 channels to meningeal pain receptors **(Borkum 2018).**

Even more confusing are the mechanisms at the basis of the interictal brain disorder that predisposes migraine patients to develop an attack. Many factors such as genetic background**,** nitric oxide hypersensitivity**,** lack of cortical habituation**,** and a disturbed energy metabolism may determine the migraine threshold **(Olesen 2008, De Vries et al. 2009, and Reyngoudt et al. 2011a)**.

Patients with migraine may have variants in nuclear genes involved in mitochondrial function or have particular haplotypes, polymorphisms, or mitochondrial double stranded deoxyribonucleic acid (DNA) mutations **(Koga and Nataliya 2005 and Sparaco et al. 2006).** Alteration in the brain excitability in migraine has been hypothesized, based on genetic mutations and/or polymorphisms of chromosomes **(Becerra et al. 2016).** Many magnetic resonance spectroscopy (MRS) studies have been performed in migraine patients and showed an interictal energy disturbance in the brain of migraine patients **(Reyngoudt et al. 2011b)**.

This may be due to dysfunction of metabolism of neuronal mitochondrial energy, NTs and ion canals of the central nervous system (CNS) **(Hardison and Yorns 2013 and Dong et al. 2017).**

Neurons are the only source of N-acetyl-aspartate (NAA). This molecule, which assesses neuronal integrity, leaves CNS through astrocytes and then it is reversed into circulation and excreted by kidney in urine samples **(Bates et al. 1996).** The NAA is considered a marker of axonal integrity. It is synthesized and located prevalently in

mitochondria of neurons and in fact it has been taken as a marker of mitochondrial functioning **(Clark 1998 and De Tommaso et al. 2012).** Prophylactic pharmacotherapy for migraine headaches is less than satisfactory, due to the lack of pathogenesis, the poor efficacy and debilitating adverse effects **(Hardison and Yorns 2013).** Identification of alterations of mitochondrial functions holds promise for better understanding migraine pathogenesis, and may help in developing new strategies for prevention and treatment of migraine.

Aim of the Study

AIM OF WORK

The aim of this study is to explore the alterations of mitochondrial functions in migraine.

Review of Literature

Chapter I

Migraine pathophysiology