Review Article
Yonsei Med J 2025 Mar;66(3):131-140
https://doi.org/10.3349/ymj.2024.0325
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Therapeutic Approach to Epilepsy in Patients with Mitochondrial Diseases

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Mitochondrial diseases (MDs) are genetic disorders with diverse phenotypes that affect high-energy-demand organs, notably the central nervous system and muscles. Epilepsy is a common comorbidity, affecting 40%–60% of patients with MDs and significantly reducing their quality of life. This review discusses the different treatment modalities for epilepsy in patients with MDs. Advances in genetic sequencing have identified specific mutations in mitochondrial and nuclear DNA, enabling more precise diagnoses and tailored therapeutic strategies. Anti-seizure medications and dietary interventions, such as ketogenic diets and their variants, have been effective in reducing seizures and improving mitochondrial function. Emerging treatments include gene therapy, mitochondrial transplantation, and antioxidants such as EPI-743, which protect mitochondrial integrity and improve neurological function. Additionally, therapies that promote mitochondrial biogenesis, such as bezafibrate and epicatechin, are being explored for their potential to enhance mitochondrial proliferation and energy production. Gene therapy aims to correct genetic defects underlying MDs. Techniques like mitochondrial gene replacement and using viral vectors to deliver functional genes have shown promise in preclinical studies. Mitochondrial transplantation, an emerging experimental technique, involves transferring healthy mitochondria into cells with dysfunctional mitochondria. This technique has been demonstrated to restore mitochondrial function and energy metabolism in preclinical models. Patient-derived induced pluripotent stem cells can model specific mitochondrial dysfunctions in vitro, allowing for the testing of various treatments tailored to individual genetic and biochemical profiles. The future of mitochondrial medicine is promising, with the development of more targeted and personalized therapeutic strategies offering hope for improved management and prognosis of mitochondrial epilepsy.

Key Words: Mitochondrial diseases, epilepsy, ketogenic diet, antioxidants, gene therapy

INTRODUCTION

Mitochondria are essential organelles that produce adenosine triphosphate (ATP) through the electron transport chain and the oxidative phosphorylation (OXPHOS) system.[1,2] Primary mitochondrial diseases (MDs) are metabolic disorders that arise from genetic mutations and cause mitochondrial dysfunction.[3-10] Recent developments in gene sequencing technology have revealed that MDs can be broadly classified according to the affected DNA: mitochondrial DNA (mtDNA) and nuclear DNA.[4,5,11-13] In addition, the phenotypic characteristics of mtDNA-related MDs can vary depending on the level of heteroplasmy. Genetic disorders characterized by mitochondrial dysfunction include Leigh syndrome spectrum; mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); neuropathy, ataxia, and retinitis pigmentosa; myoclonic epilepsy with ragged-red fibers (MERRF); myoclonic epilepsy, myopathy, and sensory ataxia; Kearns–Sayre syndrome; Alpers–Huttenlocher syndrome (AHS); and ataxia neuropathy spectrum.[8,11,14-17]

MDs can affect various organs, including the central nervous system (CNS), muscles, heart, endocrine organs, eyes, and ears. Symptoms predominantly manifest in the CNS and muscles, where mitochondria are most concentrated.[1,2,9,15] CNS symptoms include epilepsy, developmental regression, migraine,

Received: October 11, 2024 **Revised:** December 3, 2024
Accepted: December 31, 2024 **Published online:** January 23, 2025
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•The authors have no potential conflicts of interest to disclose.

myoclonus, cortical blindness, and pyramidal or extrapyramidal signs.[8-11,18] Epilepsy is a common comorbidity affecting approximately 40%–60% of patients with MDs. Mitochondrial dysfunction is an important pathophysiological factor in epilepsy, a condition that directly affects the quality of life of patients with MDs.[14,18-23] However, unlike epilepsy in patients without MDs, treatment of patients with MD requires careful consideration, as anti-seizure medications (ASMs) and diet therapies (DTs) can exacerbate mitochondrial dysfunction. Additionally, treatment to suppress seizures and strategies to improve mitochondrial dysfunction and energy depletion should be attempted simultaneously in patients with epilepsy and MDs.[15,24,25] Special strategies are required in establishing a treatment plan for epilepsy in patients with MD due to these characteristics.[12,22,26]

This review summarizes the different modalities for treating epilepsy in patients with MD and provides extensive information on these therapeutic approaches.

PATHOPHYSIOLOGY OF EPILEPTOGENESIS IN MITOCHONDRIAL DYSFUNCTION

Understanding the involvement of mitochondrial dysfunction in epilepsy requires a basic knowledge of mitochondrial structure and function. Mitochondria have a double-membrane structure, and the inner membrane houses the OXPHOS system, which contains the enzymes involved in the electron transport chain and ATP synthesis.[1,27] OXPHOS is performed by five respiratory chain complexes, including coenzyme Q10 (CoQ10) and cytochrome c.[28,29] In addition to their function in ATP production, mitochondria are directly involved fatty acid oxidation, calcium homeostasis, and programmed cell death.[29]

The mitochondria-dense brain has a high oxygen demand, making it susceptible to damage caused by oxidative stress.[30] Mitochondrial dysfunction linked to increased production of reactive oxygen species (ROS) in the brain can induce neuronal cell death, leading to epileptogenesis. Neuronal degeneration also lowers the seizure threshold.[31] Additionally, mitochondrial dysfunction may increase susceptibility to seizures by decreasing intracellular ATP levels and disrupting calcium homeostasis.[28,30] For example, mitochondrial dysfunction increases neuronal vulnerability in temporal lobe epilepsy and causes seizure-induced hippocampal cell loss in pathologic hippocampal or parahippocampal lesions.[32] Repeated seizures due to oxidative stress create a vicious cycle that exacerbates mitochondrial damage. Thus, oxidative stress plays an important role in epileptogenesis in MD-induced epilepsy, and neuronal hyperexcitability due to ATP depletion contributes to persistent, intractable seizures (Fig. 1).[31,33]

Based on this pathophysiology, patients with MDs, such as MELAS, Leigh syndrome spectrum, and MERRF, have refractory seizures as the main phenotype, and epilepsy severity may vary depending on the specific pathogenic variants or heteroplasmy.[33-37] Patients with MELAS often experience non-convulsive or convulsive status epilepticus, necessitating specific strategies for ASM development.[28,31,36] Therefore, effective epilepsy treatment in patients with MDs requires understanding the characteristics and usage of existing ASMs and excluding medications toxic to mitochondria. Additionally, medications that improve mitochondrial dysfunction or have beneficial effects on mitochondria should be considered.

THERAPEUTIC MODALITIES OF EPILEPSY IN MD

ASMs

Valproic acid

Valproic acid (VPA) has several mechanisms of action, including modulation of γ-aminobutyric acid (GABA) and glutamate pathways.[38] It is commonly used to suppress generalized and focal seizures. Particularly, it is recognized as a first-tier drug for Lennox–Gastaut syndrome (LGS).[39] Epilepsy in patients with MDs often develops into intractable epilepsy.[40] However, VPA is known for its mitochondrial toxicity, including inhibition of the mitochondrial β-oxidation pathway, mitochondrial complexes I and IV, and ATP synthesis. It can impair the structural organization of the inner mitochondrial membrane and induce carnitine deficiency.[39,41,42] Therefore, it is generally contraindicated for patients with MDs and is not the first choice ASM for these patients.[12,42] Pathogenic variants of mtDNA polymerase γ (POLG) cause AHS, and symptoms related to mtDNA depletion appear in these patients. Therefore, VPA is absolutely contraindicated to treat seizures in patients with AHS. VPA is not recommended for other MDs, except in cases such as intractable status epilepticus. Due to side effects, such as hepatotoxicity, hyperammonemia, and pancreatitis, caution is required when increasing the dose of VPA.[12,38,42]

Phenobarbital

Phenobarbital (PB) exerts an anticonvulsant effect through synaptic inhibition by acting on the $GABA_A$ receptor.[43] It is relatively safe as the first choice for neonatal seizures and is widely used in status epilepticus. According to an international Delphi-based consensus, many experts believe that oral PB is safe for epilepsy in patients with MDs.[42] However, PB can decrease ATP synthesis in mitochondria, impair state 3 respiration, and lead to mitochondrial impairment, such as impaired calcium uptake or release.[41,43] Therefore, PB is generally classified as an ASM in which mitochondrial toxicity dominates.[44] Additionally, PB may exacerbate myoclonic seizures; hence, caution should be exercised in patients with MERFF.[12,45] Given its strong sedative effect, PB should be used with caution in patients with MDs

https://doi.org/10.3349/ymj.2024.0325

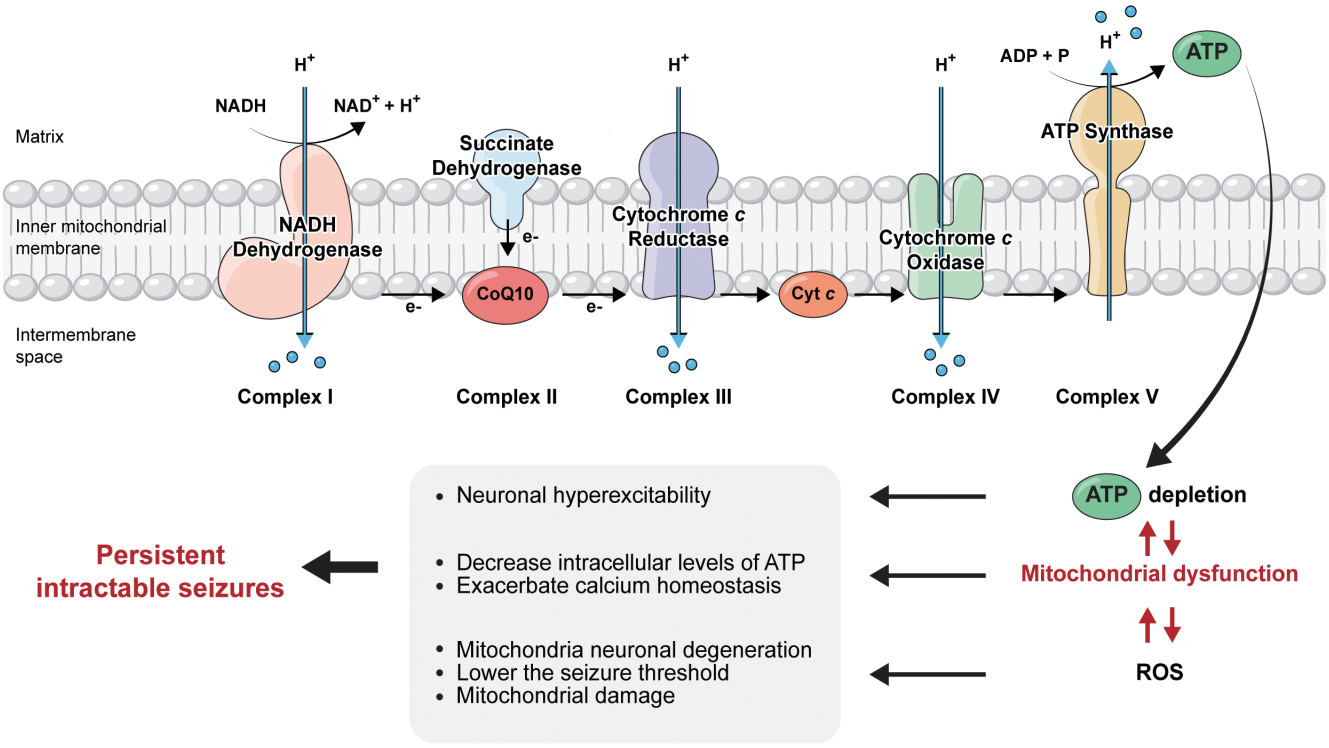

Fig. 1. Schematic diagram of the mitochondrial respiratory chain and the process by which ATP depletion due to mitochondrial dysfunction progresses to intractable seizures. The mitochondrial respiratory chain and the effect of mitochondrial dysfunction on persistent, intractable seizures are closely related to ATP production. Each complex in the chain plays a crucial role in electron transfer and proton pumping, ultimately storing energy and synthesizing ATP. A defect at any stage of this process can lead to ATP depletion, resulting in intractable seizures. ATP is essential for stabilizing cell membranes, operating ion pumps such as the sodium-potassium pump, and regulating intracellular calcium concentrations. Mitochondrial dysfunction, ATP depletion, and the production of ROS are interrelated processes that can exacerbate each other, leading to a vicious cycle of worsening cellular function. ADP, adenosine diphosphate; ATP, adenosine triphosphate; CoQ10, coenzyme Q10; Cyt c, cytochrome c; NAD, nicotinamide adenine dinucleotide (oxidized form); NADH, nicotinamide adenine dinucleotide (reduced form); ROS, reactive oxygen species.

who have brain stem lesions or respiratory problems.[43,46]

Benzodiazepines

Benzodiazepines (BZDs) exhibit anticonvulsant effects by reducing the excitability of neurons by acting on the $GABA_A$ receptor. Representative BZDs used as ASM include lorazepam, diazepam, midazolam, clonazepam, and clobazam.[12,41] BZDs demonstrate a strong anti-seizure effect in the early stage of epileptogenesis and also have an anti-anxiety effect. With relatively low mitochondrial toxicity, they are recommended for treating epilepsy in patients with MDs.[42,44] BZDs are particularly effective in controlling myoclonus in patients with MERFF.[6,45]

Phenytoin

Phenytoin (PTH) is a voltage-gated sodium channel (VGSC) blocker for focal and generalized tonic-clonic seizures.[46] Additionally, it is mainly used as a second-line ASM for status epilepticus.[42] Fosphenytoin, a water-soluble prodrug of PTH, offers a safer profile than PTH. It avoids severe local tissue damage, such as extravasation and purple glove syndrome. Additionally, it reduces the risk of cardiac arrhythmias due to its controlled conversion to PTH. PTH metabolites inhibit mitochondrial Na/K-ATPase and Mg-ATPase, decreasing the overall ATP production in mitochondria.[41,43] Additionally, severe hepatotoxicity may occur as a major side effect.[43,47] Therefore, PTH can be used in emergencies such as status epilepticus, but is not recommended as the first choice for epilepsy in patients with MDs.[41,44]

Carbamazepine and oxcarbazepine

Carbamazepine (CBZ) is a VGSC blocker primarily used for focal seizures.[46,48] However, caution should be exercised when administering CBZ to patients with MERFF, as it may exacerbate atonic and myoclonic seizures.[45] CBZ is a CYP3A4 inducer with drug interactions with other ASMs. Additionally, CBZ doubles its clearance due to its autoinduction effect, thus reducing the serum half-life. Oxcarbazepine (OXC) is a 10-keto analog of CBZ that has similar effects but fewer side effects. Additionally, OXC, unlike CBZ, does not cause autoinduction. CBZ and OXC can decrease ATP production and mitochondrial membrane potential at the cellular level.[41,43,47] Additionally, major side effects such as hepatotoxicity and hyponatremia should be considered when using these ASMs for epilepsy in patients with MDs.

Zonisamide

Zonisamide (ZNS) blocks VGSC and T-type calcium channels and acts as a weak carbonic anhydrase inhibitor.[48,49] It is effective for focal and generalized seizures and is recommended for intractable epilepsy, such as LGS and West syndrome (WS). ZNS is also effective for myoclonic seizures and is recommended for MERFF.[45] ZNS has a relatively long half-life (approximately 70 h) compared to other ASMs. Additionally, ZNS has a protective effect on mitochondria and improves mitochondrial β-oxidation; hence, unlike other ASMs, it benefits mitochondrial function.[41,44,49] However, its side effects in patients with MD who require an increased energy supply include decreased appetite, weight loss, and vomiting, necessitating monitoring during use.[48]

Lacosamide

Lacosamide (LCS) is a third-generation VGSC blocker causing slow inactivation of VGSCs, unlike other VGSC blockers.[48] Therefore, LCS exerts a smaller effect on the physiological function of neurons and a selective inhibitory effect on persistent and repetitive hyperexcitable neurons. Additionally, LCS prevents abnormal neuronal connections by binding to collapsin response mediator protein 2 (CRMP2).[48,50] Brustovetsky, et al.[50] conducted an experiment that showed that LCS acts on CRMP2 to prevent the transformation of mitochondrial morphology and motility of neurons and reported the possibility of the mitochondrial protective effect of LCS. Additionally, LCS can be safely and effectively used in patients with MELAS with drug-resistant focal epilepsy.[51] However, the effect of LCS on mitochondrial function lacks sufficient evidence. Therefore, caution should be exercised in the long-term use of LCS in epilepsy in patients with MDs.[41,44,51]

Lamotrigine

Lamotrigine (LTG) is a third-generation VGSC blocker and an effective broad-spectrum ASM for focal and generalized seizures.[39,48] LTG is preferentially used in treating intractable epilepsy, such as LGS.[25,39] Additionally, since LTG is a mood stabilizer, it can effectively replace other ASMs, which can cause excessive irritability. LTG exerts its neuroprotective effect by inhibiting proteasome inhibitor-induced apoptosis, ROS production, and depletion and oxidation of glutathione.[52] Through this molecular effect, LTG suppresses changes in mitochondrial membrane permeability and exhibits a mitochondrial protective effect by suppressing changes in the structure and morphology of mitochondria.[52,53] However, LTG can aggravate myoclonic seizures; thus, it should be used with caution in patients with MERFF. Moreover, caution is required with rapid titration of LTG due to the risk of rash.[41,45] Overall, LTG is considered the preferred ASM for patients with MD to control various types of seizures and can be used safely and effectively to treat epilepsy in MDs.[44]

Topiramate

Topiramate (TPM) is a broad-spectrum ASM that acts on various receptors and iron channels and is widely used as monotherapy or adjuvant therapy to control focal or generalized seizures.[48] TPM acts as a VGSC blocker by inhibiting the modulatory effect on the $GABA_A$ receptor, glutamate receptor, and carbonic anhydrase.[39,54] TPM exerts its neuroprotective effect through its inhibitory action on mitochondrial permeability transition pores. However, an in vitro study reported that TPM can have a side effect of inhibiting the mitochondrial zinc enzyme human carbonic anhydrase.[41,44,54] Additionally, long-term high-dose use may increase the risk of renal stone formation and kidney dysfunction. As the risk of these side effects may increase when TPM is used with ZNS, caution is required when using it for epilepsy in MDs with renal impairment, especially in patients with MELAS.[42]

Levetiracetam

Levetiracetam (LEV) is a broad-spectrum ASM that exerts its anti-seizure effect by binding to synaptic vesicle protein 2A. It is used as monotherapy or adjuvant therapy to control focal or generalized seizures. LEV has relatively minimal respiratory depressant or sedative effects, making it safe for epilepsy in patients with MDs with respiratory impairment and useful in status epilepticus.[42,46] LEV has demonstrated an endogenous antioxidative effect in the hippocampus of rats in an in vivo study, validating its neuroprotective effect.[41,44] LEV is also effective for myoclonic seizures in patients with MERRF and is the most commonly used ASM in these patients.[45] However, appropriate dose adjustment is necessary for patients with MDs and renal involvement, particularly those with MELAS carrying the m.3243A>G variant.[42]

Perampanel

Perampanel (PER) is an ASM with a novel and unique mechanism that acts as a selective antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), one of the N-methyl-D-aspartate receptors (NMDARs).[55,56] It is particularly effective in controlling intractable focal seizures. Compared with other ASMs, PER has a long half-life and fewer drug interactions, thereby making its use easy. However, an increase in dose may be required when PER is used together with a CYP3A4 inducer, such as CBZ, TRL, or PTH, as the blood PER concentration may decrease. Side effects include dizziness and somnolence, and the mitochondrial effect of PER has not yet been investigated.[41] However, several case reports have recommended PER for controlling focal seizures or refractory status epilepticus intractable to other ASMs in patients with MELAS.[24,36,55,57] Theoretically, PER targeting NMDAR and AMPAR is more effective than ASMs related to GABA in patients with status epilepticus. Further clinical studies are needed to clarify these findings and the mitochondrial effect of PER.[56,58]

https://doi.org/10.3349/ymj.2024.0325

DTs

Owing to the challenges in controlling epilepsy in MDs with ASMs, non-pharmacological treatments such as DTs are sometimes necessary.[59-61] DTs often refer to the ketogenic diet (KD) and its variants. The KD is a low-carbohydrate, high-fat diet that exerts strong anticonvulsant effects through β-oxidation and ketone body (β-hydroxybutyrate, acetoacetate, and acetone) production. The KD and its variants are dietary interventions that have been employed to manage refractory epilepsy, which is often observed in patients with MD.[60,62] These high-fat, low-carbohydrate diets induce ketosis, providing an alternative energy source for the brain and reducing seizure frequency.[63,64] The metabolic shift induced by these diets can improve mitochondrial function and energy metabolism, offering a non-pharmacologic treatment option for managing seizures. They can be divided into classic KD (fat-to-carbohydrate plus protein ratio of 4:1 or 3:1), medium-chain triglyceride diet, modified Atkins diet, and low-glycemic-index diet, based on the fat-to-carbohydrate plus protein ratio. The KD has been widely applied since its effectiveness was proven, especially in pediatric patients with intractable epilepsy, such as WS or LGS.[60,65,66]

The possible mitochondrial protective effects of the KD are as follows: reducing oxidative damage in the brain associated with metabolic stress, increasing glutathione peroxidase in hippocampal cells, decreasing mitochondrial ROS production, blocking neuronal cell death, and enhancing ATP production in the brain. Several studies have reported the mitochondrial protective effect of the KD, and the KD has been applied to patients with MD. Moreover, DT has been reported to effectively reduce seizures in patients with LGS and mitochondrial dysfunction or pyruvate dehydrogenase complex deficiency.[60,63,65] However, the results were contradictory in some studies in which DT was applied to epilepsy in patients with MDs.[61] DT may significantly worsen metabolic acidosis or cause side effects, such as vomiting, diarrhea, severe infection, renal stones, dyslipidemia, and osteoporosis, in patients with MDs. Additionally, the condition of patients with epilepsy in MDs rapidly deteriorated or resulted in death owing to DT. Particularly, caution should be exercised when applying DTs to pyruvate carboxylase deficiency and POLG-related Alpers syndrome due to a severe catabolic crisis. Clinical outcomes of DT application in patients with MDs appear to vary based on their genetic profiles, suggesting that the effectiveness of DT cannot be uniformly confirmed across all patients with MDs. Therefore, drawing clear conclusions about the efficacy and safety of DT application in MDs is challenging. Careful application of DT is essential, depending on the patient's condition.[60,61,67]

Cannabidiol

Cannabidiol (CBD) is a major component of the Cannabis plant, and products containing CBD have anti-inflammatory, anti-emetic, and anti-psychotic effects. Recently, anti-seizure effect of the pure form of CBD has been proven, and it is widely used in patients with intractable epilepsy.[68,69] Unlike other extracts of the Cannabis plant, such as tetrahydrocannabinol, CBD has been recognized for its safety since it does not have a euphoria-inducing effect. Several placebo-controlled randomized control studies have demonstrated that CBD is particularly effective in LGS and Dravet syndrome (DS), leading to its recognition as an ASM with Class I evidence for seizure control in these conditions.[70,71] In double-blind, placebo-controlled trials (GWPCARE4 and GWPCARE3) involving patients with LGS, an approximate 40% reduction in seizure frequency was observed. In GWPCARE5, an open-label study linked to these trials, the seizure frequency was reduced by 60% after 48 weeks. A similar effect was observed in the case of DS.[70-72]

The mechanism by which CBD exerts its anti-seizure effects remains unclear. Endocannabinoids play a major role in regulating neuronal firing and synaptic transmission. CBD is hypothesized to have anti-seizure effects by acting as an allosteric negative modulator of endocannabinoids. CBD inhibits intracellular calcium release and reduces neuronal hyperexcitability in epileptic neurons by antagonizing G protein-coupled receptor 55 and desensitizing the transient receptor potential of vanilloid type 1 channels. CBD also reduces neuronal excitability by modulating adenosine-mediated signaling. Additionally, CBD exerts its anti-seizure effect by acting on VGSCs, voltage-gated potassium channels, 5-HT1a receptors, and modulators of $GABA_A$ receptors.[73,74]

Growing evidence suggests that CBD is involved in the improvement of mitochondrial function. In a study using rat primary hippocampal cell culture, CBD directly affected mitochondrial respiration and exerted a mitochondrial protective effect. CBD may reduce oxidative stress and enhance mitochondrial bioenergetics in hippocampal neurons. Reports have also indicated that CBD plays a positive role in mitochondrial fission and fusion. Various experimental studies have reported that CBD helps improve mitochondrial function; however, further studies investigating its effects on mitochondria are required. KLS-13019, a derivative of CBD, affects mitochondria by enhancing mitochondrial function and providing neuroprotection. It modulates mitochondrial Na^+/Ca^{2+} exchange and reduces cellular oxidative stress, which is beneficial for conditions such as hepatic encephalopathy. Furthermore, compared with CBD, it demonstrates increased potency and safety, suggesting a promising therapeutic profile for neurological disorders.[75] Owing to the mitochondrial protective effects and stability of CBD, clinical trials are being conducted for intractable mitochondrial epilepsy, although related literature does not exist. The need for clinical studies on mitochondrial epilepsy is increasing. Table 1 summarizes therapeutic modalities for epilepsy in MD.

Emerging treatments

Recent advancements in MD treatment have focused on symp-

tomatic management and targeted therapies to enhance mitochondrial function and mitigate the consequences of mitochondrial dysfunction.[76-78] These strategies aim to address the diverse clinical manifestations of mitochondrial OXPHOS defects, which affect high-energy-demand organs, such as the nervous system, skeletal and cardiac muscles, kidneys, liver, and endocrine system. The complexity of mitochondrial disorders necessitates a multifaceted approach, integrating bio-

Table 1. Main Indications and Mitochondrial Toxicity of Various Therapeutic Modalities for Epilepsy in Mitochondrial Disease

	Main indication	Mitochondrial toxicity
Valproic acid	• Generalized seizures • Focal seizures • Lennox–Gastaut syndrome	• Inhibition of mitochondrial β-oxidation pathway, mitochondrial complexes I and IV • Inhibition of ATP synthesis • Impaired structural organization of the inner mitochondrial membrane • Induction of carnitine deficiency • Contraindication in POLG-related Alpers syndrome
Phenobarbital	• Neonatal seizures • Status epilepticus	• Decreases ATP synthesis in mitochondria • Reduces state 3 respiration • Impairment of Ca uptake/release • Should be used cautiously in MERFF due to the exacerbation of myoclonic seizures
Benzodiazepines	• Effective in the early stages of seizures	• Low mitochondrial toxicity
Phenytoin	• Focal seizures • Generalized tonic-clonic seizures • Second-line anti-seizure medication in status epilepticus	• Inhibits mitochondrial Na/K-ATPase and Mg-ATPase • Decreases overall ATP production in mitochondria • Severe hepatotoxicity may occur
Carbamazepine Oxcarbazepine	• Primarily for focal seizures	• Decreases ATP production and mitochondrial membrane potential at the cellular level • Should be used cautiously in MERFF due to the exacerbation of myoclonic seizures and atonic seizures • Hepatotoxicity and hyponatremia
Zonisamide	• Focal and generalized seizures • Lennox–Gastaut syndrome • West syndrome • Effective for myoclonic seizures in MERFF	• Can interfere with energy supply due to the side effect of decreased appetite
Lacosamide	• Primarily for focal seizures • Effective in MELAS with drug-resistant focal epilepsy	• Insufficient data
Lamotrigine	• Focal and generalized seizures	• Protective effect on mitochondria • Should be used cautiously in MERFF due to the exacerbation of myoclonic seizures and atonic seizures
Topiramate	• Focal and generalized seizures	• Reduces the risk of renal stone formation and kidney function • Low mitochondrial toxicity
Levetiracetam	• Focal and generalized seizures • Status epilepticus • Effective for myoclonic seizures in MERFF	• Low mitochondrial toxicity
Perampanel	• Intractable focal seizures • Effective in MELAS with drug-resistant focal epilepsy	• Insufficient data
Diet therapies	• Drug-resistant epilepsy • Lennox–Gastaut syndrome with mitochondrial dysfunction • Pyruvate dehydrogenase complex deficiency	• The degree of mitochondrial toxicity may vary depending on the subtype of the MD • May significantly worsen metabolic acidosis • Can cause severe catabolic crises in pyruvate carboxylase deficiency, POLG-related Alpers syndrome
Cannabidiol	• Lennox–Gastaut syndrome • Dravet syndrome	• Insufficient data • May have a protective effect on mitochondria

ATP, adenosine triphosphate; MD, mitochondrial disorder; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged-red fibers; POLG, mitochondrial DNA polymerase γ.

https://doi.org/10.3349/ymj.2024.0325

chemical, genetic, and pharmacological interventions.[79-81]

Several pharmacological agents have shown promise in enhancing the electron transfer chain function. CoQ10 is a key electron transfer chain component, facilitating electron transfer from complexes I and II to III. CoQ10 supplementation has been particularly beneficial in patients with primary CoQ10 deficiency, significantly improving clinical outcomes. The efficacy of CoQ10 in other mitochondrial disorders remains limited; however, its role in restoring electron flow is crucial.[79,82] Idebenone, a synthetic analog of CoQ10, has also demonstrated potential in improving mitochondrial function, particularly in Leber's hereditary optic neuropathy, by enhancing electron transfer and reducing oxidative stress.[79,81] These treatments represent a significant step forward in managing mitochondrial dysfunction, although more extensive clinical trials are needed to fully establish their efficacy.

Antioxidants play a vital role in mitigating the oxidative stress associated with mitochondrial dysfunction. Agents such as vitamin C, vitamin E, lipoic acid, and EPI-743 have been investigated for their ability to neutralize ROS and protect mitochondrial integrity.[79,80] EPI-743 in particular has shown promise in clinical trials, improving neurological function and reducing disease progression in patients with MDs.[83,84] The antioxidant properties of these agents help to stabilize mitochondrial membranes and reduce the damage caused by excessive ROS production, which is a hallmark of many mitochondrial disorders.[78,85] Ongoing research is exploring the optimal combinations and dosages of these antioxidants to maximize their therapeutic potential.[66,76,78,79]

Emerging therapies targeting mitochondrial biogenesis and dynamics are also under investigation. Bezafibrate, a peroxisome proliferator-activated receptor agonist, has been shown to enhance mitochondrial biogenesis and improve fatty acid oxidation.[83] This agent, along with epicatechin and RTA 408, stimulates mitochondrial proliferation and increases cellular energy production, offering potential therapeutic benefits for mitochondrial disorders. Enhancing mitochondrial biogenesis can compensate for dysfunctional mitochondria by increasing the number of healthy mitochondria in cells, thereby improving the overall cellular energy metabolism. Studies are ongoing to determine the long-term effects of these treatments and their potential use in combination with other therapeutic strategies.

Gene therapy is a cutting-edge approach aimed at correcting genetic defects causing MDs.[86,87] Techniques such as mitochondrial gene replacement and the use of viral vectors to deliver functional copies of defective genes have shown promise in preclinical studies. For instance, using adeno-associated virus vectors to deliver mitochondria-targeted genes has demonstrated efficacy in restoring mitochondrial function and ameliorating disease symptoms in animal models.[79,88] These gene therapy techniques hold the potential to provide long-term treatment by directly addressing the genetic root causes of mitochondrial dysfunction. Clinical trials are underway to evaluate the safety and effectiveness of these approaches in human patients.[83,88]

Another innovative therapeutic strategy is nucleotide bypass therapy, which involves supplementing intermediates of mitochondrial nucleotide biosynthesis pathways to bypass defective enzymes and restore nucleotide levels.[80] This approach has shown potential for conditions such as thymidine kinase 2 deficiency, where it helps maintain mtDNA integrity and improve clinical outcomes. By ensuring a steady supply of nucleotides necessary for mtDNA replication and repair, nucleotide bypass therapy can prevent the progressive decline in mitochondrial function observed in these patients. Researchers are investigating the broader applicability of this therapy for different types of MDs.

Mitochondrial transplantation is an emerging experimental technique that involves transferring healthy mitochondria into cells with dysfunctional mitochondria.[79,81] This approach has shown promise in preclinical models, where it has been used to restore mitochondrial function and improve cellular energy metabolism. Mitochondrial transplantation has emerged as a novel therapeutic approach for patients with severe MDs who do not respond to conventional treatment, although it is still in the early stages of research. Developing reliable methods for isolating and transplanting mitochondria is crucial for advancing this therapy to clinical applications.[89]

Precision medicine approaches, including the use of patient-specific induced pluripotent stem cells, are being explored to develop personalized therapies for MDs.[82] Induced pluripotent stem cells derived from patients can be used to model their specific mitochondrial dysfunctions in vitro and test the efficacy of various treatments. This personalized approach aims to tailor treatments to the individual genetic and biochemical profiles of patients, potentially improving therapeutic outcomes.[81,88] The integration of genomic data with clinical information is expected to enhance the precision of these therapies, leading to more effective and individualized treatment plans.

Ongoing research and clinical trials are paving the way for novel therapies that target various aspects of mitochondrial dysfunction, although MD treatment remains challenging. These emerging treatments, ranging from pharmacological agents and antioxidants to gene therapy and precision medicine, offer hope for improving the quality of life and disease prognosis in patients with MDs. Continued investments in research and clinical trials are essential for translating these promising therapies from bench to bedside and developing effective long-term MD treatments. The future of mitochondrial medicine is promising as we move toward more targeted and personalized therapeutic strategies.[90]

CONCLUSION

MDs often present with complex neurological manifestations, particularly epilepsy. Recent studies have highlighted the varied epileptic phenotypes associated with mitochondrial disorders, emphasizing the need for personalized and targeted treatment strategies.[91] For instance, children with early-onset MDs frequently exhibit epileptic encephalopathy with spasms and focal seizures, which can severely impact their neurological development and quality of life. LGS associated with mitochondrial respiratory chain complex I deficiency exemplifies the severe epileptic manifestations observed in patients with MDs.[92-94] These patients often experience refractory seizures and have poorer prognostic outcomes compared to individuals without such deficiencies, necessitating more aggressive and targeted therapeutic approaches.

Advancements in understanding the genetic underpinnings of MDs have opened new avenues for treatment. Identifying specific genetic mutations allows for more precise diagnostic and therapeutic strategies tailored to the individual's genetic makeup.[95] For example, gene therapy can correct underlying genetic defects, whereas mitochondrial transplantation is being explored as a method to replace dysfunctional mitochondria with healthy ones. Additionally, antioxidants and compounds that enhance mitochondrial biogenesis and function are being investigated for their potential to mitigate the effects of mitochondrial dysfunction.[89,91] Moreover, the importance of comprehensive management approaches that include dietary interventions, such as ketogenic and modified Atkins diets, which have shown efficacy in reducing seizure frequency in patients with mitochondrial epilepsy, is growing. Neurostimulation therapies, such as vagus nerve stimulation (VNS), offer nonpharmacological options that can significantly enhance the quality of life for patients. While evidence specific to mitochondrial disorders is limited, VNS may be beneficial, reducing seizure frequency and overall improving quality of life for some patients.[93]

Integrating these emerging therapies into clinical practice is critical, and ongoing research is essential to validate their efficacy and safety. Clinical trials and longitudinal studies will play pivotal roles in optimizing treatment protocols and improving outcomes for patients with mitochondrial epilepsy. Continued investment in research to translate these promising therapies from the laboratory to the clinic is urgently required to ensure that patients receive the most effective and personalized care.[91]

Overall, while mitochondrial epilepsy presents significant treatment challenges, advancements in genetic research, therapeutic strategies, and comprehensive care approaches provide a positive outlook for the future. Continued research and clinical efforts are imperative to harness these developments to improve the management and prognosis of mitochondrial epilepsy.

ACKNOWLEDGEMENTS

We would like to express our sincere appreciation to the patients with mitochondrial disease, their families, and the medical staff members. Additionally, we are profoundly thankful to the generous donors whose financial support and interest in treating rare neurodegenerative diseases have made this research possible.

MID (Medical Illustration & Design), as a member of the Medical Research Support Services of Yonsei University College of Medicine, provided excellent support with medical illustration.

AUTHOR CONTRIBUTIONS

Conceptualization: Ji-Hoon Na and Young-Mock Lee. Data curation: Ji-Hoon Na and Young-Mock Lee. Formal analysis: Ji-Hoon Na and Young-Mock Lee. Funding acquisition: Young-Mock Lee. Investigation: Ji-Hoon Na. Methodology: Ji-Hoon Na. Project administration: Ji-Hoon Na. Resources: Ji-Hoon Na and Young-Mock Lee. Software: Ji-Hoon Na. Supervision: Young-Mock Lee. Validation: Young-Mock Lee. Visualization: Ji-Hoon Na. Writing—original draft: Ji-Hoon Na. Writing—review & editing: Ji-Hoon Na. Approval of final manuscript: all authors.

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