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Overview of Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episodes (MELAS) syndrome

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Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episode (MELAS) is a rare maternally inherited disorder primarily caused by mutations in mitochondrial DNA, notably the m.3243A>G mutation in the *MT-TL1* gene. This mutation impairs mitochondrial function crucial for cellular energy production, particularly in high-energy-demanding organs such as the brain and muscles. MELAS manifests as recurrent stroke-like episodes, seizures, diabetes mellitus, cardiomyopathy, and other multisystemic symptoms that are often present in childhood. The diagnosis combines genetic testing, clinical evaluation, and neuroimaging, with elevated lactate levels and characteristic magnetic resonance imaging (MRI) findings as key indicators. Treatment focuses on symptomatic management and enhancement of mitochondrial function through L-arginine, coenzyme Q10, high-dose vitamins, and taurine supplementation. Studies have identified additional genetic variants linked to MELAS, including mutations in POLG and other mitochondrial genes, further complicating the genetic landscape. Emerging therapies, particularly gene therapy and mitochondria-targeting drugs, offer promising avenues for addressing the underlying genetic defects and improving mitochondrial functioning. Furthermore, ongoing studies continue to enhance our understanding and management of MELAS, with the aim of reducing its burden and improving patient outcomes and quality of life. This review summarizes the current knowledge on the genetics, clinical features, diagnosis, and treatment of MELAS, highlighting the latest advancements and future directions for therapeutic interventions.

Key words: MELAS syndrome, Mitochondrial disease, Mitochondrial encephalomyopathy, Stroke-like episode, DNA, Mitochondrial

Introduction

Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episodes (MELAS) is a rare maternally inherited disorder that primarily affects the nervous system and muscles[1]. It typically manifests during childhood after a period of normal development, with onset usually occurring between ages 2-15 years. MELAS is characterized by recurrent encephalopathy, myopathy, seizures, migraine-like headaches, and focal neurological deficits[2,3]. Moreover, there have been documented cases where symptoms had manifested

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either in infancy or much later between ages 15–40 years[1,3,4].

The genetic basis of MELAS is primarily linked to mutations in mitochondrial DNA (mtDNA), with the m.3243A>G mutation in the *MT-TL1* gene being the most common, accounting for approximately 80% of the cases. Another significant mutation is m.3271T>C[1,5], which causes impaired mitochondrial function crucial for cellular energy production, particularly affecting organs with high energy demands, such as the brain and muscles[1,6,7]. Diagnosing MELAS involves a combination of clinical evaluation, genetic testing, and neuroimaging. MRI often reveals cortical infarcts that do not correspond to typical vascular territories. However, genetic testing for mtDNA mutations confirms the diagnosis[8,9]. Treatment of MELAS focuses on managing the symptoms and its diverse clinical manifestations. Therapeutic strategies often include the administration of agents, such as L-arginine, carnitine, and coenzyme Q10, which are thought to support mitochondrial function[1,9,10].

This review aimed to provide a comprehensive overview of the genetic and clinical features of MELAS, highlighting the latest advancements in its diagnosis and management. By synthesizing the current knowledge, we hope to enhance the understanding and care of individuals with this challenging mitochondrial disorder.

Overview and genetics of MELAS

MELAS is a rare, maternally inherited mitochondrial disorder primarily caused by mutations in mtDNA. Mitochondria are known as cell powerhouses and are critical for energy production via oxidative phosphorylation (OXPHOS). MELAS typically results from mutations that impair OXPHOS function, leading to multisystemic effects, especially in metabolically active organs, such as the brain, heart, muscles, and eyes[1,10].

The prevalence of MELAS varies with the population. Among adult Finnish population, the prevalence of the m.3243A>G mutation has been reported to be 10.2 per 100,000. In Northern England, the prevalence of this mutation in the adult population is approximately 1 in 13,000 individuals. However, these figures may have been underestimated because a comprehensive study of a large Caucasian population in 2006 revealed a prevalence of 236 per 100,000 individuals for the m.3243A>G mutation[10,11].

The maternal inheritance pattern of MELAS is due to the fact that paternal mitochondria are present only in the tailpiece of sperm, which is lost during fertilization. Consequently, all mitochondria in the offspring originate from the mother. Although MELAS is generally inherited, there are rare instances of sporadic MELAS without a family history[12].

One of the most prevalent genetic mutations associated with MELAS is the m.3243A>G mutation in the *MT-TL1* gene, which encodes tRNALeu. This single-nucleotide variation is present in approximately 80% of patients with MELAS. Another common mutation, m.3271T>C, was observed in approximately 10% of the cases. These mutations disrupt the normal assembly of proteins into respiratory chain complexes, impair OXPHOS, and reduce cellular energy production[3,11,12].

Besides *MT-TL1* mutations, ongoing studies have identified other genetic variants linked to MELAS. Mutations in *POLG* and *BCS1L* are associated with similar phenotypes. Furthermore, while the m.3243A>G mutation is the most common cause of MELAS, other mtDNA and nuclear gene mutations such as those in *POLG* can lead to similar stroke-like episodes. Additionally, other mitochondrial genes, including *MT-TL2* (encoding $tRNA^{Leu(CUN)}$), *MT-TK* (encoding $tRNA^{Lys}$), *MT-TH* (encoding $tRNA^{His}$), *MT-TQ* (encoding tRNAGln), *MT-TF* (encoding tRNAPhe), *MT-TV* (encoding tRNAVal), *MT-ND1, MT-ND4, MT-ND5, MT-ND6* (encoding subunits of complex I), *MT-CO2, MT-CO3* (encoding subunits of complex

IV), and *MT-CYB* (encoding a subunit of complex III), have also been implicated. This genetic diversity underscores the complexity of MELAS and variability in its clinical presentation[1,3,11-14].

MELAS is characterized by heteroplasmy, meaning that both normal and mutant mtDNAs coexist within the cells. This leads to variability in disease severity and symptom presentation because different tissues may have different proportions of mutated mtDNA. Consequently, the clinical manifestations of MELAS vary widely, even among patients with the same mutation. The most commonly affected tissues are those with high metabolic demand, including the brain, skeletal muscles, heart, eyes, and ears. Diagnostic challenges arise from this heteroplasmy, as serum and urine tests may not always detect abnormalities if affected cell lines are not present in these samples. In such cases, a muscle biopsy is often necessary to identify the disease[1,7].

Several theories have been proposed to explain MELAS pathogenesis. The cytopathic theory suggests that mitochondrial mutations lead to abnormal OXPHOS, resulting in neuronal dysfunction and cell death during periods of high metabolic activity. This theory explains why highly active brain regions, such as the visual cortex, are often affected early and more severely. The angiopathic theory explains that mitochondrial dysfunction in vascular endothelial cells leads to impaired autoregulation and neuronal ischemia, contributing to the symptoms of the disease[1,3,15].

Neurological symptoms of MELAS are thought to result from transient OXPHOS dysfunction within the brain parenchyma. Both parenchymal and vascular abnormalities in OXPHOS may contribute to the multisystem involvement observed in MELAS. An OXPHOS defect increases free radical production, potentially causing vasoconstriction and offsetting vasodilators, such as nitric oxide (NO)[6]. Patients with MELAS exhibit impaired NO production and sequestration, leading to NO deficiency. This deficiency, combined with impaired mitochondrial energy production and microvascular angiopathy, may cause impaired cerebral vasodilation[15,16].

MELAS is characterized by recurrent metabolic strokes, often with onset before the age of 40 years, although a later onset is also recognized. Prodromal symptoms include headaches and visual disturbances, which can precede focal neurological deficits or seizures. MRI reveals cortical and subcortical lesions that do not correspond to typical vascular territories. MRI proton spectroscopy often shows elevated lactate levels in the affected regions and ventricular cerebrospinal fluid[1,16].

Diagnosis of MELAS

Genetic testing is necessary for confirming MELAS. Mutations in the mitochondrial DNA, particularly *MT-TL1*, are commonly associated with this disorder[1]. Next-generation sequencing techniques have significantly improved the detection of these mutations with high sensitivity and specificity[3,13]. Recent advances in molecular diagnostics have introduced new methodologies such as whole-exome sequencing and mitochondrial DNA copy number analysis, which can detect a broader spectrum of genetic abnormalities[13]. These techniques can provide a quick and more accurate diagnosis, allowing timely intervention and management.

Neuroimaging plays a vital role in diagnosing MELAS. Brain MRI often reveals stroke-like lesions that do not conform to vascular territories, which is a distinguishing feature of the syndrome[9]. These lesions can change over time, reflecting the transient nature of stroke-like episodes in patients[9]. Additionally, MRI can detect elevated lactate levels in the brain, further supporting its diagnosis[13].

Although invasive, muscle biopsies can provide

definitive diagnostic information. Histological examination often reveals ragged-red fibers, a characteristic finding of mitochondrial myopathies. Electron microscopy can reveal abnormal mitochondrial morphology[9]. Additionally, biochemical assays of muscle tissues can measure the activity of the respiratory chain complexes, which are typically reduced in patients with MELAS. Blood tests and muscle biopsies also reveal elevated lactate and pyruvate levels, which are indicative of mitochondrial dysfunction[1].

Diagnosis of MELAS requires a combination of clinical, radiological, genetic, and biochemical evaluations. Early recognition and accurate diagnosis are essential for effectively managing the disease and improving patient outcomes[1,9,13]. Ongoing studies and advancements in genetic testing continue to enhance our understanding of the diagnostic capabilities of this challenging mitochondrial disorder.

Clinical manifestation of MELAS

The clinical manifestations of MELAS underscore the complexity and multi-system nature of the syndrome, necessitating a multidisciplinary approach for management and treatment to address the diverse and severe symptoms experienced by patients.

1. Neurologic Manifestation

MELAS syndrome is primarily characterized by their profound impact on the nervous system. Patients often present with stroke-like episodes that manifest as a sudden-onset hemiparesis, hemianopsia, and cortical blindness, frequently accompanied by lactic acidosis and seizures[14-17]. These stroke-like episodes are recurrent and can lead to chronic progressive encephalopathy, resulting in significant cognitive decline and dementia over time[3,15]. Seizures are another common neurological manifestation of both the focal and generalized types. A notable proportion of patients experience status epilepticus, a severe and prolonged seizure condition that can be fatal[3,4,18]. Additionally, neuroimaging often reveals multiple scattered cortical lesions and cerebral atrophy, which correlates with the clinical severity of the disease[16] (Fig. 1).

2. Endocrinological Manifestation

Endocrinological abnormalities are a significant aspect of MELAS. Diabetes mellitus is particularly prevalent, affecting approximately 85% of patients with the m.3243A>G mutation by the age of 70[17]. This high prevalence is attributed to mitochondrial dysfunction

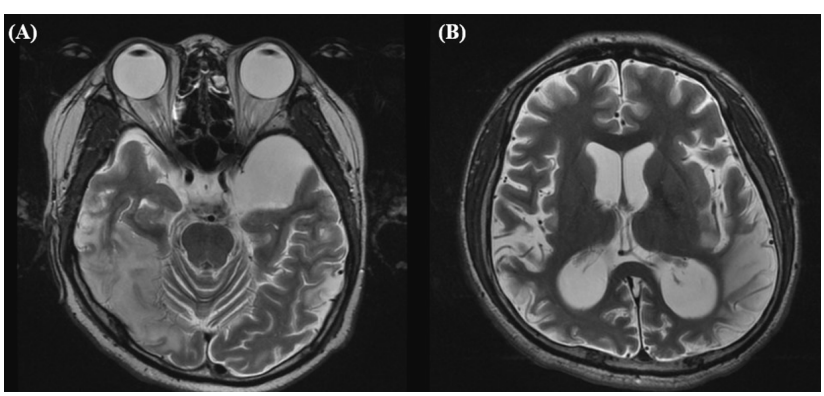

Fig. 1. Brain MRI findings of MELAS. T2 Axial Image of a 27-Year-Old Male patient with MELAS syndrome. (A) Cerebromalacic changes are observed in the right temporo-parieto-occipital lobe.. (B) Old MELAS involvement is noted in the left parietal lobe, accompanied by generalized brain atrophy and lateral ventriculomegaly.

in pancreatic beta cells, leading to impaired insulin secretion and subsequent hyperglycemia. Besides diabetes, other endocrinological manifestations include growth hormone deficiency, which results in short stature and delayed puberty, highlighting the extensive systemic effects of mitochondrial dysfunction on endocrine organs[4]. These manifestations often complicate the overall disease management and require a complex approach for effective treatment.

3. Cardiovascular Manifestation

Cardiac involvement in MELAS is significant and multifaceted, often presenting as hypertrophic cardiomyopathy, which can progress to dilated cardiomyopathy and heart failure if not properly managed[15]. Arrhythmias, including Wolff-Parkinson-White syndrome and ventricular tachycardia, are common and contribute to an increased risk of sudden cardiac death[16]. The myocardial pathology of MELAS includees increased mitochondrial inclusions, abnormal crista structures, and widespread cardiomyocyte damage, which collectively impairs cardiac function[15]. Electrocardiographic abnormalities and findings of reduced ejection fraction and ventricular hypertrophy were also frequently observed, indicating the need for regular cardiac monitoring in these patients[18].

4. Skeletal and muscular manifestations

Muscle involvement in MELAS is characterized by exercise intolerance and muscle weakness due to the high energy demands of skeletal muscles and their dependency on mitochondrial ATP production. Patients typically present with myopathy, marked by muscle atrophy, elevated serum creatine kinase levels, and fatigue[4]. Muscle biopsies often reveal ragged-red fibers, indicative of abnormal mitochondrial proliferation, and various other histopathological changes, such as fiber size variation and increased lipid storage[3,18]. These muscular manifestations can severely affect a patient's quality of life, necessitating interventions to manage symptoms and maintain mobility.

5. Gastrointestinal Manifestation

Gastrointestinal symptoms in MELAS include recurrent vomiting, abdominal pain, and chronic constipation, often linked to gastroparesis and pseudo-obstruction caused by smooth muscle involvement[1,4]. These gastrointestinal issues are exacerbated by the involvement of the autonomic nervous system, leading to dysmotility and severe nutritional deficiencies. Pancreatic dysfunction, as evidenced by the high prevalence of diabetes mellitus, further complicates gastrointestinal manifestations and requires comprehensive nutritional and metabolic management to address these challenges[17].

6. Other Manifestations

MELAS syndrome includes various other systemic manifestations. Sensorineural hearing loss is common, and results from mitochondrial dysfunction in the cochlea, which can lead to progressive deafness[16]. Visual impairments such as retinopathy cause gradual vision loss due to retinal ganglion cell degeneration[1,16]. Renal disorders are another significant symptoms, with patients presenting with proteinuria and renal tubular acidosis, indicating the broader multiorgan impact of MELAS[3]. These additional manifestations underscore the complexity of the syndrome and necessity for a holistic approach to patient care.

Treatment of MELAS

The complicated treatment regime for MELAS underscores the complexity of managing this multisystem disorder and highlights the necessity for a comprehen-

sive multidisciplinary approach to optimize patient outcomes. By addressing the diverse symptoms and underlying mitochondrial dysfunction, these treatments can potentially improve the quality of life and prognosis of patients with MELAS (Table 1).

1. Symptomatic Treatment

Symptomatic treatment of MELAS primarily targets the management of stroke-like episodes and seizures that are prevalent in patients. Anti-seizure medications (ASMs) such as valproate, levetiracetam, and lamotrigine are commonly used to control seizures, which significantly affects the quality of life of patients with MELAS[19,20]. Stroke-like episodes, characterized by acute neurological deficits, are managed with L-arginine and citrulline supplementation, which promotes NO production and enhances cerebral blood flow, thereby reducing the severity and duration of these episodes[2,21]. In addition, Q10 and idebenone have been used to support mitochondrial functions. These compounds are thought to improve OXPHOS and reduce the frequency of stroke-like episodes by enhancing mitochondrial energy production[4,21]. Symptomatic treatment also includes the management of migraine-like headaches, which are treated with standard migraine therapies, such as triptans and beta blockers[19].

2. High-Dose Multi-Vitamin Treatment

High-dose multi-vitamin therapy is another cornerstone of MELAS treatment, particularly the administration of the vitamin C, E, and B complex. This treatment helps reduce oxidative stress and improve mitochondrial function as oxidative damage is a significant component of MELAS pathology[4]. Vitamin C and E are potent antioxidants that help neutralize free radicals and reduce oxidative stress within the mitochondria.

Table 1. Treatment options for MELAS

	Mechanism	Dose
L-arginine and citrulline supplementation	Promotes NO production and enhances cerebral blood flow	Children: 500 mg/kg Adults: 10,000 mg/m^2 body surface area/day
CoQ10 supplementation	An electron transporter crucial for the function of the mitochondrial respiratory chain	Children: 2-8 mg/kg/day Adults: 200-600 mg/day
L-carnitine supplementation	Essential for the transport of long-chain fatty acids into the mitochondria for beta-oxidation	Children: 20-100 mg/kg/day Adults: 1,000-3,000 mg/day
High-Dose Multi-Vitamin Treatment		
Thiamine (B1)	Essential components of the pyruvate dehydrogenase complex	Children: 10 mg/kg/day Adults: 300-1,000 mg/day
Riboflavin (B2)	Serves as a precursor of flavoproteins involved in the electron transport chain	50-400 mg/day
Niacin (B3)	Precursor of NAD+ and NADP+	Children: 25-250 mg/day Adults: 250-1,000 mg/day
Pyridoxine (B6)	Pyridoxine is metabolized to pyridoxal phosphate, a cofactor of several mitochondrial enzymes	25 mg/day
High-Dose Taurine Treatment	Critical role in modifying mitochondrial $tRNA^{Leu}$ (UUR)	40 kg or more: 12,000 mg/day 25-39 kg: 9,000 mg/day 15-24 kg: 6,000 mg/day less than 15 kg: 3,000 mg/day

Abbreviations: NAD+, Nicotinamide adenine dinucleotide; NADP+, Nicotinamide adenine dinucleotide phosphate.

B-complex vitamins, including thiamine (B1), riboflavin (B2), niacin (B3), and pyridoxine (B6) are crucial for various enzymatic reactions in mitochondrial energy metabolism. Thiamines are essential components of the pyruvate dehydrogenase complex, which links glycolysis to the citric acid cycle and enhances ATP production[2,22]. Riboflavin serves as a precursor of flavoproteins involved in the electron transport chain, whereas niacin is a precursor of NAD+ and NADP+, which are vital for redox reactions during cellular metabolism[4,21,22].

3. High-Dose Taurine Treatment

Taurine supplementation has emerged as a promising treatment for the prevention of stroke-like episodes in patients with MELAS. High-dose taurine, administered at doses of 9-12 grams per day, has shown significant efficacy in reducing the frequency of stroke-like episodes[20,22,23]. The rationale behind taurine supplementation is its role in modifying mitochondrial $tRNA^{Leu}$ (UUR), which is defective in MELAS due to the m.3243A>G mutation. This modification is crucial for accurate mitochondrial protein synthesis and high-dose taurine supplementation has been shown to restore this modification, thereby improving mitochondrial function[20]. Clinical studies have demonstrated that taurine can decrease the annual relapse rate of stroke-like episodes from 2.22 to 0.72, highlighting its potential as a therapeutic agent for the management of MELAS[20,22].

4. Other Treatments

Besides the standard treatments, several other therapies are being explored for MELAS. Dichloroacetate (DCA) is a treatment that lowers lactic acid levels by activating the pyruvate dehydrogenase complex, thereby improving mitochondrial energy metabolism[22]. L-carnitine supplementation is another treatment option that supports fatty acid oxidation and enhances ATP production in mitochondria. L-carnitine is essential for the transport of long-chain fatty acids into the mitochondria for beta-oxidation, and its supplementation has been shown to improve exercise tolerance and reduce muscle fatigue in patients with MELAS[1,2,4]. Antioxidants such as alpha-lipoic acid and N-acetylcysteine have been studied for their potential to reduce oxidative damage and support mitochondrial function[1,2].

5. Research on Emerging Treatments

Research on emerging treatments for MELAS is ongoing, focusing significantly on gene therapy and novel pharmacological agents. Gene therapy aims to correct the underlying mitochondrial DNA mutations responsible for MELAS. Experimental approaches include the use of mitochondria-targeted nucleases and gene editing technologies, such as CRISPR/Cas9, to repair or replace defective mitochondrial DNA[22]. Another promising area of research involves the use of compounds that enhance mitochondrial biogenesis and function. EPI-743 (a synthetic analog of CoQ10) and elamipretide (a mitochondria-targeting peptide) have been investigated for their potential to improve mitochondrial health and reduce clinical manifestations of MELAS[22]. These drugs stabilize the inner mitochondrial membrane and enhance electron transport chain function, thereby improving cellular energy production and reducing oxidative stress[22,23].

Conclusion

MELAS is a complex and multifaceted mitochondrial disorder that manifests with various clinical symptoms, including recurrent stroke-like episodes, seizures, diabetes mellitus, and cardiomyopathy. These manifestations reflect the profound impact of mitochondrial dysfunction on metabolically active tissues, such as the brain, heart, and muscles. Current treatments focus on

alleviating these symptoms and improving mitochondrial function through symptomatic treatment, high-dose vitamin therapy, and innovative approaches, such as high-dose taurine supplementation. Emerging treatments, particularly gene therapy and mitochondria-targeting drugs, offer promising new avenues for addressing underlying genetic mutations and enhancing mitochondrial health. As our understanding of MELAS deepens, advancements in genetic testing and therapeutic interventions have the potential to significantly improve patient outcomes. The future of MELAS treatment is promising, with ongoing research paving the way for more effective and targeted therapies, ultimately aiming to reduce the burden of this debilitating disorder and enhance the quality of life of affected individuals[22,23].

요 약

MELAS 증후군은 다양한 임상 증상을 나타내는 복잡하고 다면적인 미토콘드리아 질환으로, 반복적인 뇌졸중 유사 에피소드, 발작, 당뇨병, 심근병증 등을 포함한다. 이러한 증상들은 뇌, 심장, 근육과 같은 대사적으로 활발한 조직에 미토콘드리아 기능 장애가 미치는 심각한 영향을 반영한다. 현재의 치료는 이러한 증상을 완화하고 미토콘드리아 기능을 개선하는 데 중점을 두고 있으며, 증상 치료, 고용량 비타민 요법 및 고용량 타우린 보충과 같은 혁신적인 접근 방식을 포함한다. 유전자 치료 및 미토콘드리아 표적 약물 분야의 새로운 치료법은 근본적인 유전자 돌연변이를 해결하고 미토콘드리아 건강을 향상시킬 수 있는 유망한 새로운 길을 제공한다. MELAS에 대한 이해가 계속 깊어짐에 따라, 유전자 검사 및 치료적 개입의 발전은 환자의 결과를 크게 개선할 가능성을 갖고 있다. MELAS 치료의 미래는 낙관적이며, 진행 중인 연구는 더 효과적이고 표적화된 치료법을 위한 길을 열어 이 질환의 부담을 줄이고 영향을 받는 개인들의 삶의 질을 향상시키는 것을 목표로 하고 있다.

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Conflict of interest

The authors declare no financial relationships or potential conflicts of interest.

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