



Clinical features, pathogenesis, and management of stroke-like episodes due to MELAS

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Abstract

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) is a disease that should be considered as a differential diagnosis to acute ischemic stroke taking into account its onset pattern and neurological symptoms, which are similar to those of an ischemic stroke. Technological advancements in neuroimaging modalities have greatly facilitated differential diagnosis between stroke and MELAS on diagnostic imaging. Stroke-like episodes in MELAS have the following features: (1) symptoms are neurolocalized according to lesion site; (2) epileptic seizures are often present; (3) lesion distribution is inconsistent with vascular territory; (4) lesions are common in the posterior brain regions; (5) lesions continuously develop in adjacent sites over several weeks or months; (6) neurological symptoms and stroke-like lesions tend to be reversible, as presented on magnetic resonance imaging; (7) the rate of recurrence is high; and; (8) brain dysfunction and atrophy are slowly progressive. The m.3243ANG mutation in the *MT-TL1* gene encoding the mitochondrial tRNA^{Leu}(UUR) is most commonly associated with MELAS. Although the precise pathophysiology is still unclear, one possible hypothesis for these episodes is a neuronal hyperexcitability theory, including neuron–astrocyte uncoupling. Supplementation, such as with L-arginine or taurine, has been proposed as preventive treatments for stroke-like episodes. As this disease is still untreatable and devastating, numerous drugs are being tested, and new gene therapies hold great promise for the future. This article contributes to the understanding of MELAS and its implications for clinical practice, by deepening their insight into the latest pathophysiological hypotheses and therapeutic developments.

Keywords Mitochondrial disease · MELAS · Stroke-like episodes · tRNA modification disorder · Neuronal hyperexcitability · Taurine supplementation

Highlights • Lesion distribution is inconsistent with vascular territory.

- MELAS tends to present spontaneous reversibility of both neurological symptoms and stroke-like lesions, but both of those are prone to relapse later.
- The m.3243ANG mutation in the *MT-TL1* gene encoding the mitochondrial tRNA^{Leu}(UUR) is commonly associated with MELAS.
- The mutation affects the taurine modification of tRNA and impairs protein synthesis.
- Neuronal hyperexcitability is a hypothesized cause of these episodes.
- Taurine administration is a new, practical, and therapeutic approach for MELAS.
- New gene therapies hold great promise for the future.

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Introduction

Cerebrovascular diseases (e.g., cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage) are commonly referred to as *strokes*, which generally develop suddenly and often present with an acute onset of neurological symptoms. The diagnosis in the clinical setting begins by asking patients and those around them the details about the condition at the time of onset. However, non-stroke diseases may also present with similar onset patterns and clinical symptoms. These diseases may be contraindicated for the same treatment as that for stroke; thus, care must be taken to distinguish between them.

One study has reported that 25% of 354 patients consecutively admitted to a stroke care unit had diseases other than stroke, as diagnosed by a non-specialist. Thus, when diagnosing stroke, clinicians must also keep these other diseases in mind (Rønning and Thommessen 2005). Generally, the

frequency of stroke-mimicking diseases is about 15%–25%, and their diagnosis can greatly vary depending on the evaluator and timing of the evaluation (Gargalas et al. 2017; McClelland et al. 2019). The accuracy of stroke diagnosis is about 50%–60% in the emergency services department and improves to about 75%–85% in the initial treatment department and specialized stroke department. By adding image inspection, the frequency of diagnosing a stroke-mimicking disease as a stroke is greatly reduced; the frequency after brain computed tomography (CT) is 4%–5%, and after brain magnetic resonance imaging (MRI), it is 1%–2% (Davis et al. 2006; Vilela 2017).

However, in the case of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), it is often difficult to distinguish this disease from acute ischemic stroke despite the close examination of its onset and diagnosis. In this article, we review the body of research on MELAS.

Features of MELAS

MELAS is a typical mitochondrial disease in that it is caused by abnormal metabolism in the mitochondria. Other mitochondrial diseases include myoclonus epilepsy associated with ragged-red fibers, Kearns–Sayre syndrome, and Leber’s hereditary optic neuropathy (LHON), which is the first disease associated with a mitochondrial DNA (mtDNA) point mutation. MELAS is characterized by hyperlactic acidosis, headache with nausea and vomiting similar to migraine, epilepsy, and stroke-like episodes, and in 1984, Pavlakis et al. (1984) proposed the concept of this disease.

Biochemically, in MELAS, the activity of Complex I nicotinamide adenine dinucleotide–coenzyme Q reductase and Complex IV cytochrome c oxidase, which are involved in the electron transport chain of mitochondria, is decreased. Such a decrease impairs the production of adenosine triphosphate (ATP), which is the energy required for cell activity. Symptoms are more likely to appear in the skeletal muscle and central nervous system, which are highly dependent on ATP produced by mitochondria. Table 1 presents the frequency of the clinical symptoms and complications of MELAS based on previous research and analyses, and the clinical findings can vary from case to case, and patients with the

m.3243A > G mutation in MELAS are at increased risk for hypertension, with a reported rate of about 50% (Hirano and Pavlakis 1994; Yatsuga et al. 2012; El-Hattab et al. 2015; Pauls et al. 2020).

Numerous cases of MELAS develop by the time patients reach adulthood, with frequent epileptic seizures and stroke-like neurological symptoms. Biochemical tests can show elevated levels of lactate and pyruvate in the blood and cerebrospinal fluid. At the time of a stroke-like attack, brain neuroimaging findings suggest ischemia or edema showing a low absorption area on CT and a high signal area on MRI, including fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted image (DWI), which are similar to a lesion found in cerebral infarction.

In 1990, Goto et al. identified the adenine-to-guanine transition at position 3243 of mtDNA (m.3243ANG) in the *MT-TL1* gene encoding transfer RNA (tRNA)^{Leu}(UUR) as the causative gene of MELAS (Goto et al. 1990). About 80% of patients with MELAS have this point mutation, but many other gene mutations have also been reported. Although mtDNA is maternally inherited, the mothers of patients with MELAS are often asymptomatic or have mild symptoms even with mutant mtDNA. This is because mtDNA is in a heteroplasmy state, in which mutant and wild types are mixed, and the proportion of mutant types is low in mothers. Moreover, the differences in the proportion of mutants due to heteroplasmy are observed not only within individuals but also within organs, tissues, and cells, indicating that cell function is impaired when the proportion of mutants exceeds a certain threshold. The clinical picture is also diversified by this heteroplasmy. Despite the existence of full-blown MELAS clinical presentation, which consists of mitochondrial encephalomyopathies, lactate acidosis, and stroke-like episodes (Yatsuga et al. 2012), the majority of m.3243A > G patients have a blinder phenotype, which implies that many carriers are clinically asymptomatic or have only mild disease not recognized as mitochondrial (Pickett et al. 2018). Although the gene mutations in MELAS have been elucidated, the pathological mechanism from mutation to stroke-like episodes is often unclear.

Recent studies have demonstrated that mitochondrial disease is one of the most prevalent groups of hereditary neurological diseases. The minimum prevalence rate for mtDNA mutations is 1 in 5,000, and the nuclear mutations

Table 1 Frequency of symptoms in patients with MELAS

Frequency	Symptom and complication
≥ 80%	stroke-like episode, seizure, disturbance of consciousness, cognitive impairment
60%–79%	visual field defect, vision impairment, headache, muscle weakness, short stature
40%–59%	sensitive deafness, general fatigue, psychiatric involvement, hypertension
20%–39%	hemiplegia, cardiomyopathy, gait disturbance, teichopsia, speech disturbance
< 20%	cerebellar ataxia, cardiac conduction disorders, diabetes mellitus

for mitochondrial disease clinically affect 2.9–9.2 per 100,000 adults (Schaefer et al. 2008; Gorman et al. 2015). One study has found that 16.5 in 100,000 unaffected children and adults younger than the retirement age have a risk for developing mitochondrial disease (Schaefer et al. 2008). The m.3243A > G mutation responsible for MELAS is the most common pathogenic mtDNA point mutation, with a minimum prevalence of 3.5 of 100,000 people (Gorman et al. 2015).

Responsibility lesion and symptoms of stroke-like episodes

Researchers are still developing the pathophysiology for the stroke-like episodes of MELAS. However, clinically, MELAS has the following characteristics:

- It presents with neurolocalization symptoms according to lesion site.
- It is often accompanied by epileptic seizures.
- The distribution of stroke-like lesions is inconsistent with a vascular territory.
- The lesions are common in the posterior brain regions (i.e., the temporoparietal junction and the parietal and occipital lobes).
- The cerebral cortex is preferentially involved, with bright thickened cortical bands showing on FLAIR images.
- The lesions continuously develop to adjacent sites over several weeks or months.
- Patients with MELAS tend to present spontaneous reversibility in both neurological symptoms and stroke-like lesions.
- Both neurological symptoms and stroke-like lesions are highly recurrent.
- Brain dysfunction and atrophy slowly progress.

Contrarily, in ischemic stroke, the lesions consistent with the cerebrovascular control area are observed on neuroimaging, and once captured on the image, the lesions do not disappear. Hemiplegia and dysarthria, which are typical stroke symptoms, are not common in MELAS. Even if those are observed, they are often caused by the effects of transient Todd's paralysis, which is a complication following seizures or cerebral edema (Demarest et al. 2014).

As mentioned above, the lesion sites of MELAS are mostly in the posterior brain regions, but clinical symptoms can also reflect disorders in these brain regions. Cortical blindness, Anton syndrome, prosopagnosia, and regional geographic disorientation have been reported as visual symptoms of the occipital lobe (Kolb et al. 2003; Alemdar et al. 2007). Cases of sensory aphasia and auditory agnosia as symptoms of temporal lobe lesions have been reported, as

have cases with constitutional disorders, left–right agnosia, and dysgraphia as symptoms of parietal lobe and related brain area lesions (Almasi et al. 2017; Tetsuka et al. 2017).

Figures 1 and 3 present the images of our MELAS cases (Tetsuka et al. 2017). A 68-year-old female patient developed convulsive seizures and was admitted to our hospital for epilepsy. Although she was an older adult, we suspected MELAS and detected elevated levels of pyruvic and lactic acids. A genetic test revealed a point mutation in the mtDNA (m.3243A > G) that led to a definitive diagnosis. However, the patient had been hospitalized twice in the previous year for suspected acute ischemic stroke and seizures.

At age 67 (in May 2014), the patient was admitted to another hospital for a suspected acute ischemic stroke, and a brain MRI there revealed hyperintensity in the left posterior temporal lobe (Fig. 1A, B, and C) (Tetsuka et al. 2017). No evident paralysis of the limbs was observed, but the patient exhibited a disturbance of consciousness and convulsive seizures. Five months after the previous admission (in October 2014), the patient was admitted to the same hospital for the same symptoms and received treatment for an acute ischemic stroke, for which a brain MRI revealed hyperintensity in the right posterior temporal lobe (Fig. 1D, E, and F) (Tetsuka et al. 2017). DWI and FLAIR of the brain MRI showed an acute ischemic stroke-like hyperintensity in the posterior part of the left temporal lobe, but previous MRI findings of the right posterior temporal lobe's hyperintensity had disappeared. Similarities exist between the hyperintensity of DWI observed in the acute phase of seizure-induced lesions and that for an ischemic stroke. The abnormal signal of DWI in seizures is not caused by hypoxia/anoxia present during acute ischemic stroke but instead by a combination of impaired energy metabolism and hemodynamic changes. Therefore, DWI observed in seizures is often reversible (Shaw et al. 2012). MRI findings in the chronic phase are characterized by a variety of endpoints, including hypoperfusion, gadolinium enhancement, and regression of hyperintensities. Some stroke-like lesions tend to be spontaneously reversible, suggesting that neuronal and glial damage has not yet reached the point of irreversible damage (Finsterer and Aliyev 2020).

Figure 2 presents the single-photon emission CT (SPECT) and arterial spin labeling (ASL)-MRI at the time when an acute ischemic stroke-like lesion appeared with hyperintensity on the DWI and FLAIR sequence (Hongo et al. 2019). A significant increase in blood flow is observed at the lesion site in both SPECT and ASL-MRI (Fig. 2C and F), and this finding is clearly different from that for an acute ischemic stroke. In addition, normal and spontaneous brain activity in patients with MELAS was assessed using functional MRI in the recent study, and the reduction in brain activity was much more extensive than in stroke-like lesions (Wang et al. 2020).

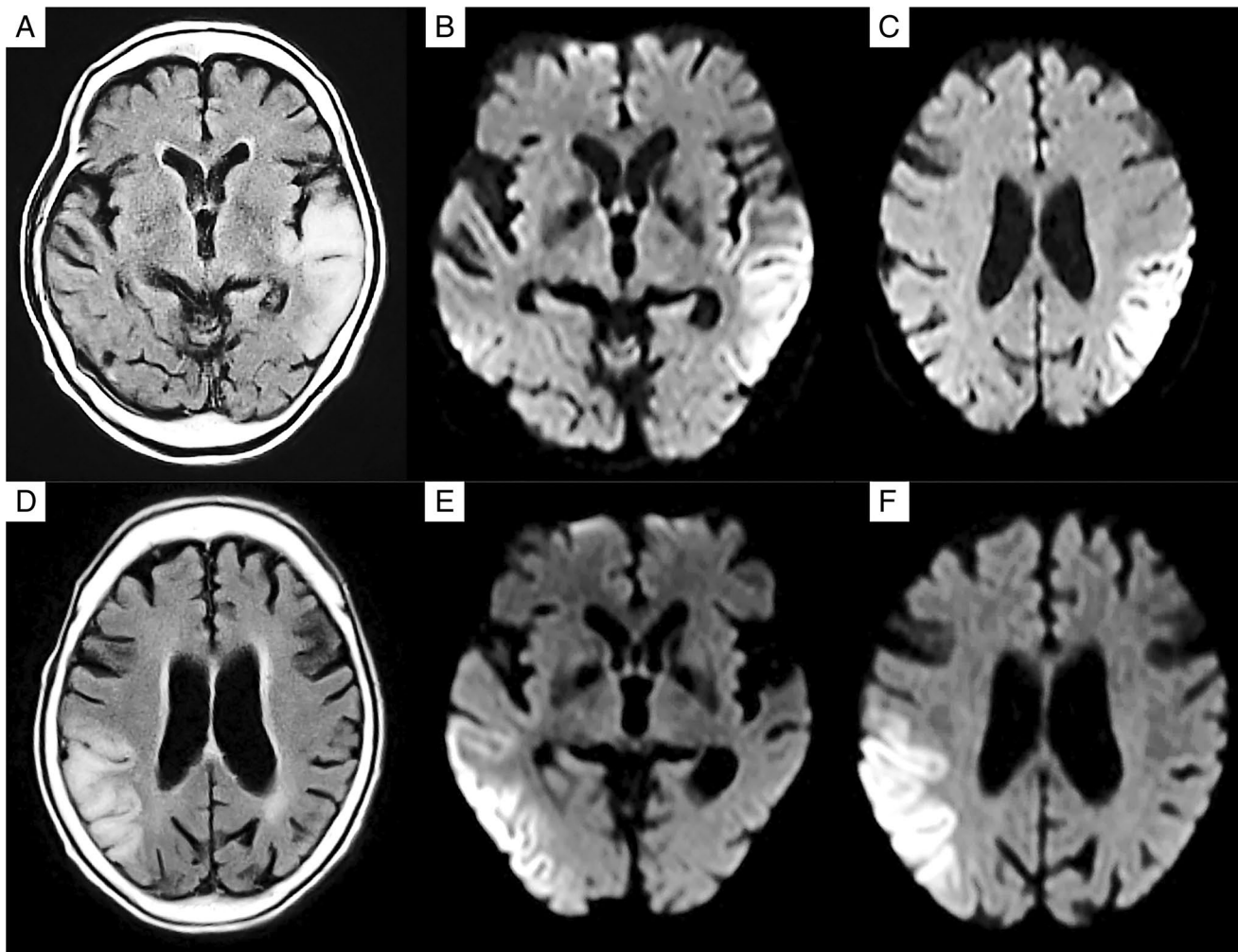


Fig. 1 (A, B and C): MRI examinations from May 2014 showing the MELAS migratory lesions. Cortical FLAIR (A) and DWI (B and C) sequences revealed hyperintensity in the left temporal lobe. (D, E and F): MRI examinations from October 2014 showing the MELAS

migratory lesions. Cortical FLAIR (D) and DWI (E and F) sequences revealed hyperintensity in the right temporal lobe. Previous MRI findings of lesions on the right posterior temporal lobe had disappeared until the second admission after 5 months

A CT scan of the head revealed calcification around the basal ganglia (Fig. 3A and B) (Tetsuka et al. 2017). Mitochondrial disease is likely to be associated with abnormal calcium metabolism, and one study has reported that MELAS has been associated with calcification of the basal ganglia, occurring in up to 13% of cases (Majamaa et al. 1998). Although basal ganglia calcification is a common incidental finding in neuroimaging of older patients, this sign should enable clinicians to consider an underlying mitochondrial disease in the presence of other appropriate clinical features (Ciafaloni et al. 1992). As the disease state progresses, cerebral atrophy is a common feature of mitochondrial disease in childhood and adulthood (Fig. 3C) (Kim et al. 2009; Tetsuka et al. 2017). In a study of brain atrophy in MELAS patients using voxel-based morphometry, a significant decrease in gray matter volume was observed

in the temporal subgyral regions (TsujiKawa et al. 2016). The cortical hyperintense signal during subacute or chronic stage compatible with cortical laminar necrosis pattern, this MRI finding is observed by a high incidence in patients with MELAS, suggesting a neuronal vulnerability (Fig. 3D) (Iizuka et al. 2002).

As stroke-like lesions and brain atrophy as shown on the MRI spread slowly and progressively, Cognitive impairment develops in 40%–90% of patients with MELAS (Hirano and Pavlakis 1994; Yatsuga et al. 2012; El-Hattab et al. 2015). Damage to neurons throughout the brain due to mitochondrial dysfunction and cerebral cortex damage accumulated by stroke-like episodes can lead to cognitive impairment with impaired intelligence, language, perception, attention, and memory functions. On neuroimaging, despite the relatively mild frontal lobe abnormalities, executive dysfunction

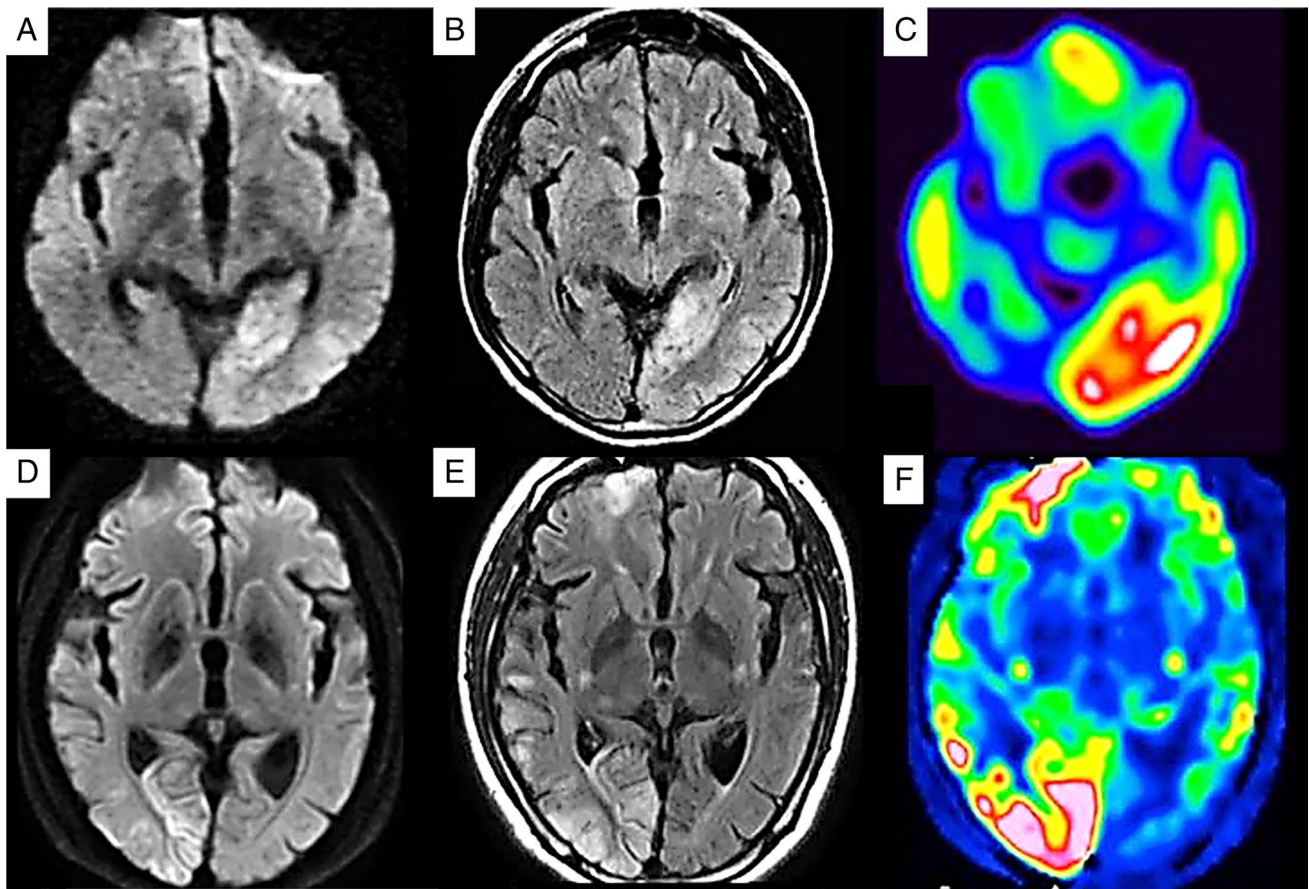


Fig. 2 Neuroimaging of adult-onset MELAS. Brain MRI (A, B) and 123I-IMP SPECT (C). DWI (A) and FLAIR (B) reveal slight hyperintensity in the left occipitotemporal cortex, and 123I-IMP SPECT marked hyperperfusion in the left occipitotemporal cortex (C). DWI (D) and FLAIR (E) demonstrate slight hyperintensity in the right

medial frontal lobe and right occipital lobe, both of which are accompanied by focal hyperperfusion on the ASL-MRI (F). The figure was cited and reprinted by modifying from the reference (Hongo et al. 2019). Permission to reuse the figures has been granted by the publisher (Springer Nature)

has been observed in patients with MELAS, suggesting a diffuse progressive neurodegeneration in addition to the damage caused by the stroke-like episodes (Sproule and Kaufmann 2008; El-Hattab et al. 2015). A recent study of cognitive impairment in MELAS patients with the m.3243A > G mutation showed a characteristic pattern of cognitive impairment: impaired attention, visual construction ability, and executive function and suggested that cognitive impairment in MELAS patients is caused in part by neurodegeneration and disturbances of brain metabolism (Kraya et al. 2019).

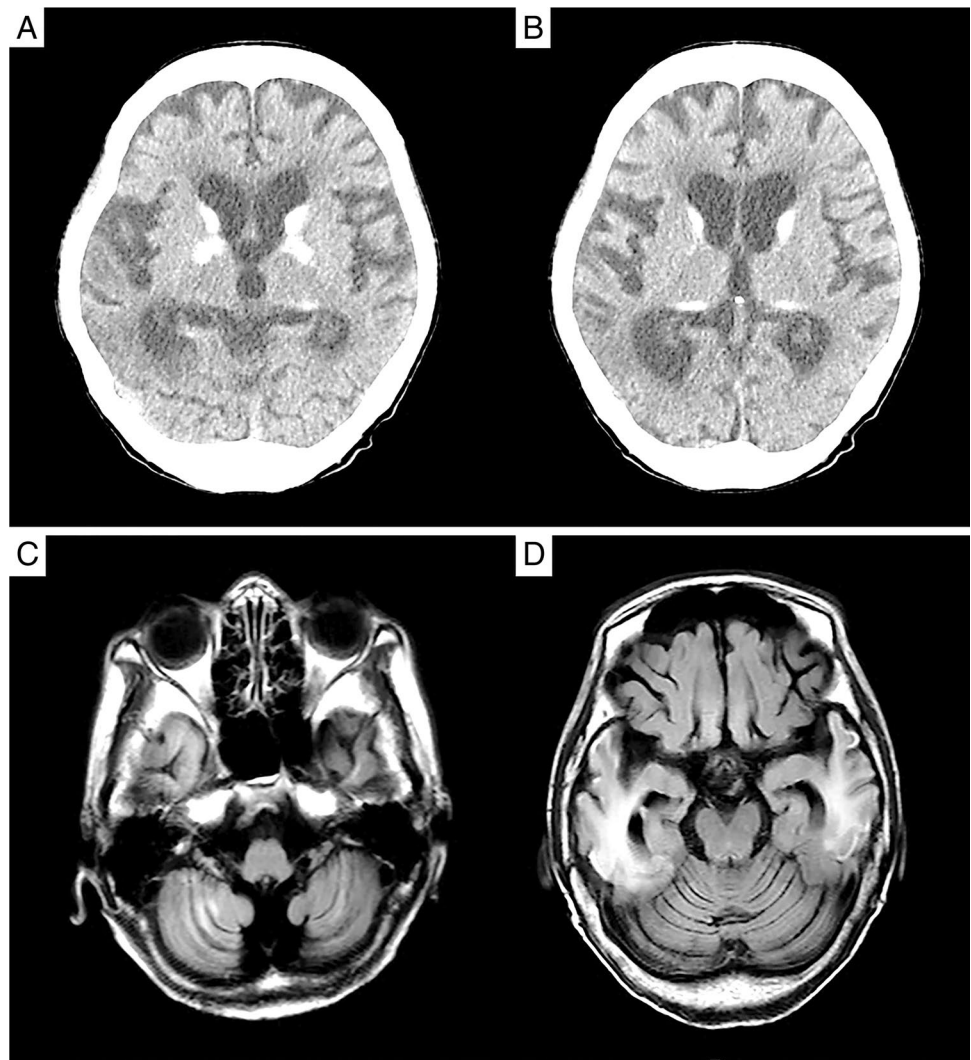
Seizure is another common neurological symptom that occurs in nearly 70%–90% of patients with MELAS (Hirano and Pavlakis 1994; Iizuka and Sakai 2010; Yatsuga et al. 2012; El-Hattab et al. 2015), which is a high frequency when compared with the incidence of early seizure accompanied by a stroke (8.9%) (Bladin 2000). In a study with 28 patients with MELAS, seizure or status epilepticus developed in 11 patients within 1 week after the onset of

stroke-like episodes (Iizuka and Sakai 2010). However, some patients with MELAS can develop seizures without the finding of stroke-like lesions on the MRI (El-Hattab et al. 2015). Despite frequent, localized stroke-like episodes, both partial and generalized seizures can occur at about the same frequency (Iizuka and Sakai 2010). A high incidence of seizures during stroke-like episodes may suggest that the excitability of cortical neurons in the acute stroke-like lesions is higher in the active phase of these episodes compared with the interictal phase.

Pathogenesis of stroke-like episodes

Gene mutations such as the A3243G point mutation in mtDNA have been reported to cause MELAS; these mutations impair taurine modification at the first base of the anticodon of the tRNA against the wobble base pair (UUG). The mutant tRNA molecules are deficient in the uridine

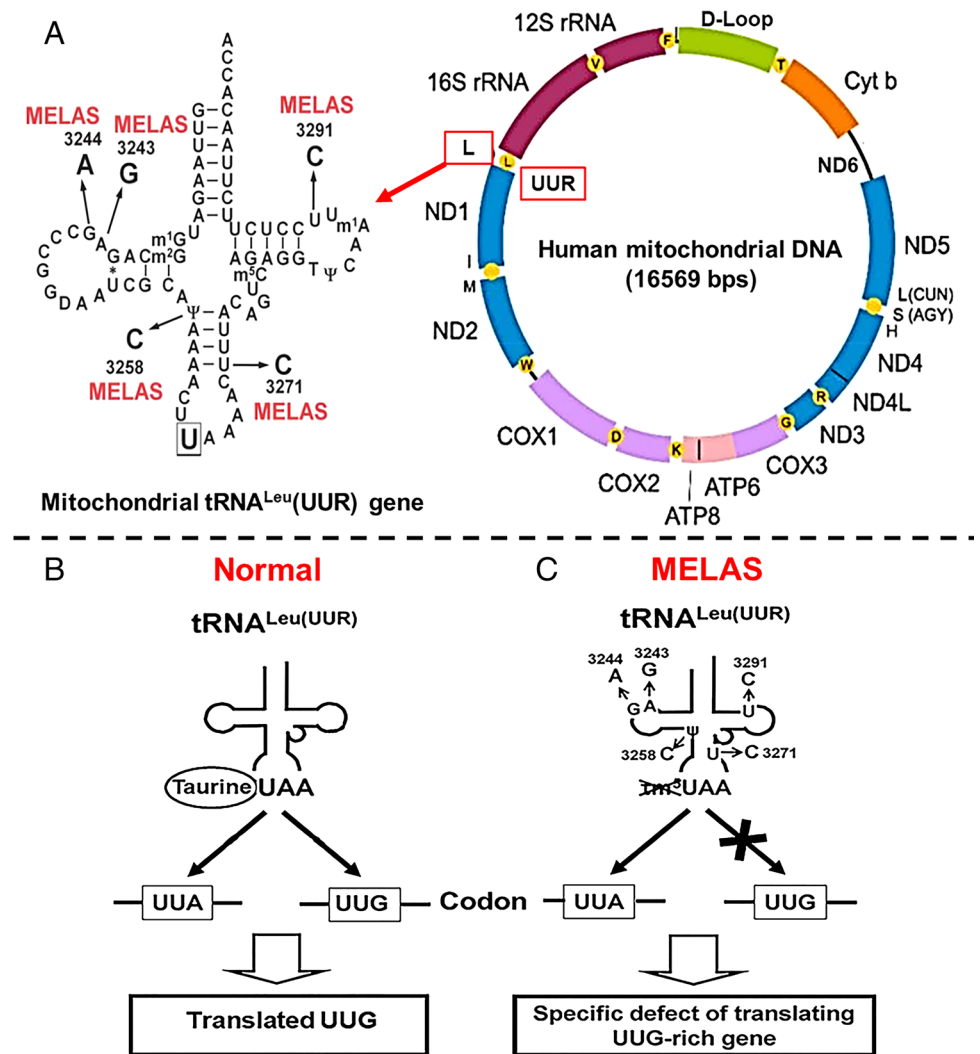
Fig. 3 CT scan of the brain from April 2016 of a patient with MELAS. In retrospect, the additional clinical features and bilateral basal ganglia calcification (**A** and **B**) are suggestive of MELAS. MRI of the brain from April 2016 of a patient with MELAS. (**C**) Cortical atrophy was prominently recognized in the cerebellar cortex. FLAIR (**D**) sequences revealed white matter and cortical laminar necrosis-like findings and cortical atrophy in the left temporal lobe



modification occurring in normal tRNA^{Leu}(UUR) at the first position of the anticodon wobble nucleotide. These modification defects can lead to the mistranslation of leucine into non-cognate phenylalanine codons by the mutant tRNA^{Leu}(UUR) (Yasukawa et al. 2000; Tsutomu et al. 2011). The pathogenic point mutation associated with MELAS is thought to prevent recognition by the tRNA-modifying enzymes. Taurine modification defects can lead to tRNA dysfunction, and human diseases caused by aberrant RNA modifications are now referred to as *RNA modopathy*, with MELAS being one of them (Torres et al. 2014; Asano et al. 2018). When translating a wobble base codon UUG, the codon can normally be recognized correctly by taurine modification of the first base of the corresponding tRNA, but research has demonstrated that the A3243G point mutation lacks taurine modification of tRNA during protein synthesis, resulting in unrecognized codon UUG and impaired protein synthesis (Fig. 4) (Yasukawa et al. 2001; Tsutomu et al. 2011; Kotrys and Szczesny 2019).

However, the detailed pathological mechanism from impaired protein synthesis to stroke-like episodes has not been completely elucidated. Current theories explaining the mechanisms of stroke-like episodes include the mitochondrial angiopathy (vascular hypothesis) and mitochondrial cytopathy theories. The former is the theory of ischemic angiopathy caused by mitochondrial abnormalities inside the vascular smooth muscle cells and vascular endothelial cells on the cerebral surface arterioles and soft membrane arterioles. The latter is the theory of intracellular metabolic disorders caused by mitochondrial dysfunction (Iizuka and Sakai 2005). Regarding the vascular hypothesis, this theory assumes that when stroke-like episodes occur, a focal impairment of the cerebral arteries ensues. However, this has been inconsistent because magnetic resonance angiography (MRA) has usually been considered normal, with no arterial dilatation, significant stenosis, spasm, or dissection in any cerebral artery (Finsterer and Aliyev 2020). A recent systematic review has proposed the possibility of alterations in the

Fig. 4 (A) Map of the human mitochondrial genome and the secondary structure of tRNA^{Leu}(UUR) associated with MELAS. (B and C) Distinct patterns of codon recognition identified in mutant tRNAs without wobble modification. (B) Normally, the taurine modification of uracil, the anticodon UAA of tRNA^{Leu}(UUR), can accurately recognize UUA as well as UUG and translate it into leucine. (C) Pathogenic point mutations (A3244G, G3244A, T3258C, T3271C, and T3291C) in mutant tRNA^{Leu}(UUR) of patients with MELAS causes a modification deficiency that results in a UUG codon-specific translational defect and induces impaired protein synthesis. The figure is cited by modifying from the references (Tsutomu et al. 2011; Kotrys and Szczesny 2019). Permission to reuse the figures has been granted by the publisher



caliber of major cerebral vessels on MRA during stroke-like episodes and the reversibility of vessel caliber alterations, which could play an important role in the pathophysiology of stroke-like lesions by altering intracranial hemodynamics (Gramegna et al. 2021). Mitochondrial metabolic dysfunction in the smooth muscle and endothelial cells of cerebral arteries may result in vessel caliber alterations, leading to mitochondrial angiopathy.

In addition, the excitability of neurons is enhanced because a stroke-like episode is likely to be accompanied by a convulsive attack. Therefore, neuronal hyperexcitability has been proposed as a pathological condition of a stroke-like episode (Iizuka and Sakai 2005). Furthermore, because acute ischemic stroke-like lesions expand to the surrounding cerebral cortex following a seizure, the epilepsy-like excitability of neurons is also considered to be involved in the expansion of lesion sites (Iizuka et al. 2003). The neuronal hyperexcitability theory predominantly assumes astrocyte dysfunction caused by ATP deficiency as the important mechanism. Astrocyte dysfunction causes poor

uptake of glutamine via glutamate transporters and of Na⁺/K⁺ ATPase-mediated potassium into astrocytes. In addition, elevated glutamine and potassium levels in the synaptic cleft can induce not only vasodilation in cerebral small vessels but also neuronal cell death due to excitotoxicity (Fig. 5) (Haddy et al. 2006; Attwell et al. 2010; Iizuka and Sakai 2010; Chen et al. 2020). Given the spread of lesions with hyperperfusion beyond the arterial region (Fig. 2), stroke-like episodes are more likely to result from neuronal hyperexcitability than from mitochondrial angiopathy.

Furthermore, the substances used by neurons as an energy source under normal conditions include both glucoses taken up from outside the cell and lactic acid supplied from astrocytes by the astrocytneuron lactate shuttle (ANLS). Conversely, when the excitability of the neurons and the energy demand increase, the energy source becomes dependent on lactic acid derived from ANLS, which is used to produce ATP in the mitochondria (Pellerin et al. 2007). In addition, astrocytes activate themselves when they sense an increase in glutamate concentration in the synaptic cleft, that is, the

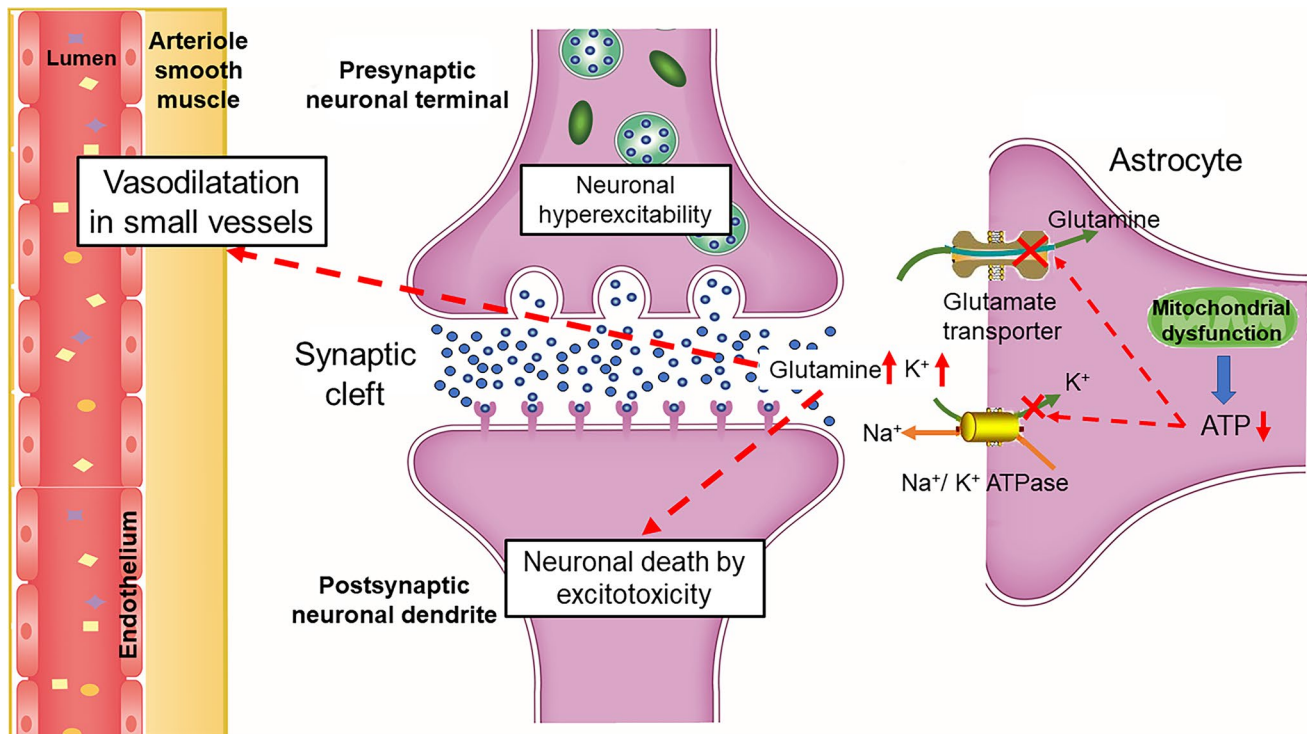


Fig. 5 Neuronal hyperexcitability theory for MELAS predominantly assumes astrocyte dysfunction caused by ATP deficiency. Astrocyte dysfunction causes poor uptake of glutamine via glutamate transporters and of Na⁺/K⁺ ATPase-mediated potassium into astrocytes. Moreover, elevated glutamine and potassium levels in the synaptic cleft can induce not only vasodilation in cerebral small vessels but also neuronal cell death due to excitotoxicity. The oxygen metabolism of

neurons and glucose metabolism of astrocytes are not coupled, resulting in a state of “neuron–astrocyte uncoupling,” and the prolongation of this condition is the pathological condition of the stroke-like episodes. Furthermore, astrocytes act on blood vessels to increase cerebral blood flow, but neurons cannot produce sufficient ATP, and the metabolism cannot keep up, resulting in an intracellular metabolic imbalance and damage to the cerebral cortex

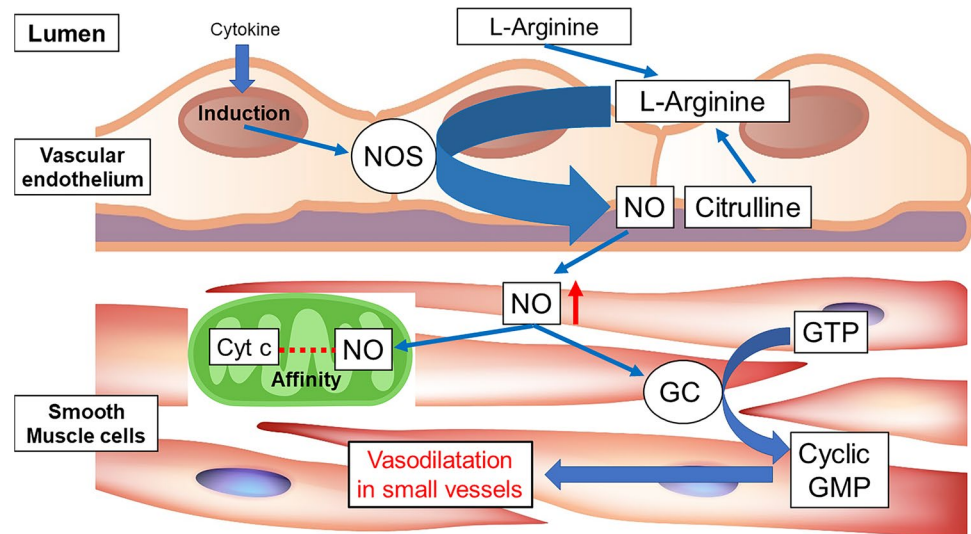
activity of the neurons releases vasodilators and increases cerebral blood flow (Fig. 5). The action of these astrocytes synchronizes the increase and decrease of cerebral blood flow with brain activity and is referred to as *neurovascular coupling* (Iadecola 2017).

In MELAS, sufficient ATP cannot be produced to satisfy the energy demand, or the supplied lactic acid cannot be fully utilized due to the disorder of oxidative phosphorylation in the mitochondria. However, in the acute phase of stroke-like episodes, lactate supply from the astrocytes via ANLS increases. In other words, the oxygen metabolism of the neurons and the glucose metabolism of the astrocytes are not coupled, thus resulting in a state of “neuron–astrocyte uncoupling.” The prolongation of this condition may be the pathological condition of the stroke-like episodes. Moreover, astrocytes act on blood vessels to increase cerebral blood flow, but neurons cannot produce sufficient ATP, and the metabolism cannot keep up, resulting in an intracellular metabolic imbalance and damage to the cerebral cortex (Fig. 5) (Iizuka and Sakai 2005).

In MELAS, in addition to energy depletion, nitric oxide (NO) deficiency occurs, and research has demonstrated

that this deficiency significantly influences the complication of the disease (El-Hattab et al. 2014). Nitric oxide synthase (NOS) is an enzyme that catalyzes the conversion of L-arginine to citrulline, and NO is also produced from L-arginine via NOS (Fig. 6). NOS mediates endothelium-dependent vascular relaxation. There are three known isoforms of NOS: two isoforms constitutively expressed (constitutive NOS), and inducible NOS, which becomes extremely abundant when stimulated by cytokines (Stuehr 1999). Citrulline is transformed into arginine by arginine succinate synthase and arginine succinate lyase. Therefore, both citrulline and arginine are required to produce NO. NO produced by vascular endothelial cells can relax vascular smooth muscle, which is necessary to maintain the patency of small vessels (Attwell et al. 2010). In MELAS, NO deficiency can result in impaired hemoperfusion in the microvasculature of various organs, thus affecting the etiology of some complications (El-Hattab et al. 2014). Decreased arginine and citrulline, which are NO precursors, can significantly affect impaired NO production. Decreased NO production can also result from the decreased activity of NOS

Fig. 6 Nitric oxide synthase (NOS) mediates endothelium-dependent vascular relaxation. NOS is an enzyme that catalyzes the conversion of L-arginine to citrulline. In the cerebrovascular endothelial smooth muscle cells, Nitric oxide (NO) binds to guanylate cyclase (GC) and converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (GMP). This process leads to the relaxation of the smooth muscle cells and vasodilation of the blood vessels. NO has a strong affinity for cytochrome c (Cyt c). In patients with MELAS, NO binding is increased, and NO availability is reduced



caused by the overproduction of reactive oxygen species (ROS) due to the impaired electron transport chain (Desquiret-Dumas et al. 2012). Furthermore, oxidative stress caused by mitochondrial dysfunction can result in an increase in asymmetric dimethylarginine, an endogenous NOS inhibitor (El-Hattab et al. 2012). In the cerebrovascular endothelial smooth muscle cells, NO binds to guanylate cyclase and converts guanosine triphosphate to cyclic guanosine monophosphate (Fig. 6). This process leads to the relaxation of the smooth muscle cells and vasodilation of the blood vessels. NO has a strong affinity for cytochrome c in mitochondria, and the vascular endothelial cells and smooth muscle cells in patients with MELAS exhibit excessive activity of cytochrome c. As a result, NO binding is increased, and NO availability in the endothelial and smooth muscle cells is reduced (Fig. 6). Hemodynamic and metabolic stress further enhances NO mobilization and reduces circulating NO levels. NO deficiency causes episodes such as hypoxemia, seizure, and stroke in patients with MELAS (Vos et al. 2001). On the other hand, it has been reported that various cytokines in the cerebrospinal fluid are elevated in the acute phase of stroke-like attacks (Emsley and Tyrrell 2002). A recent study by utilizing induced pluripotent stem cells (iPSCs) derived from MELAS patient showed that the up-regulation of the expression levels of inflammatory genes such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, Interleukin-8 and Interleukin-6 in endothelial cells (MELAS iPSCs) (Pek et al. 2019). Considering these results, we can assume that because cytokines cause a NO-elevating effect, the resulting increased NO may cause vasodilatation in small vessels and hyperperfusion, leading to trigger a stroke-like episodes in MELAS.

Management

Ubidecarenone, which is referred to as *coenzyme Q*, as an electron transport donor and Vitamins C and E as free radical scavengers may be administered to patients with MELAS, but currently, no radical treatment exists (Glover et al. 2010). Recently, L-arginine and taurine have been reported to be useful for suppressing stroke-like episodes, and future development is expected.

As mentioned above, NO exerts a vasodilatory effect, and L-arginine is a precursor of NO. Therefore, during a stroke-like attack, a decrease in L-arginine impairs arterial dilation, which might lead to cerebral ischemia. Furthermore, the administration of L-arginine to patients with MELAS results in vasodilation and might be effective in treating stroke-like episodes. In one clinical trial, L-arginine (0.5 g/kg) was administered intravenously during the acute phase of a total of 34 stroke-like episodes to 24 patients with MELAS. As a result, the scores of the subjective symptoms for headache, nausea, vomiting, visual field abnormalities, hemiplegia, and scintillating scotch improved in almost all cases within 30 min to 24 h after administration (Koga et al. 2005). Furthermore, 6 MELAS patients with frequent strokes were treated with oral L-arginine (0.15–0.3 g/kg/day) for 18 months as a preventive treatment for these strokes. As a result, the frequency of attacks per month was significantly reduced after administration (0.09 ± 0.09 times) than before administration (0.78 ± 0.42 times) (Koga et al. 2005).

In addition, in a 2-year clinical trial and a 7-year follow-up study, the systematic administration of oral and intravenous L-arginine to 15 and 10 patients with MELAS, respectively, was conducted prospectively (Koga et al.

2018). Oral L-arginine therapy prolonged the interictal phase ($p=0.0625$) and reduced the incidence and severity of ictuses, and intravenous L-arginine therapy decreased the incidence of four major symptoms, namely, headache, nausea/vomiting, impaired consciousness, and visual disturbance. Furthermore, the systematic administration of L-arginine to patients with MELAS significantly improved their survival rate and maintaining the plasma arginine concentration of at least 168 mmol/l can prevent the ictuses (Koga et al. 2018). Although large-scale randomized controlled trials are required to better evaluate the efficacy of using L-arginine treatment for stroke-like episodes, these results can bring hopeful expectations to patients with MELAS (Ng et al. 2019).

As mentioned above, the MELAS mutation causes a disorder of taurine modification of the mitochondrial tRNA^{Leu} (UUR) in the *MT-TL1* gene, and MELAS and taurine deficiency have been reported to be similar. The symptoms of MELAS, such as myocardial damage, diabetes, failure to thrive, hearing loss, muscle weakness, motor intolerance, and retinopathy, commonly appear in taurine deficiency in humans and various animals. Moreover, MELAS and taurine deficiency may have a common pathological mechanism (Schaffer et al. 2013). Rikimaru et al. conducted basic experiments and clinical studies on patients with MELAS to determine if high doses of taurine could improve neurological function and symptoms (Rikimaru et al. 2012). First, when taurine was added to cybrid cells into which mtDNA derived from MELAS patients was introduced, an increase in oxygen consumption, recovery of the decreased membrane potential, and reduction of oxidative stress were observed. In addition, when taurine (0.25 g/kg/day) was administered to two MELAS patients who had repeated seizures and stroke-like episodes, no recurrence of the seizures or episodes was observed thereafter. Serum lactic acid and pyruvate levels also decreased, and no new cerebral infarction-like lesions appeared on the MRI (Rikimaru et al. 2012).

Furthermore, a Phase III clinical trial of high-dose taurine supplementation has evaluated its efficacy for the prevention of the stroke-like episodes of MELAS (Ohsawa et al. 2019). In the trial, 10 patients with MELAS received oral high-dose taurine (9 or 12 g per day) for 52 weeks. As a result, six patients demonstrated complete elimination of their stroke-like episodes, and taurine reduced the annual relapse rate of these episodes from 2.22 to 0.72 ($p=0.001$). A significant increase in the taurine modification of mitochondrial tRNA^{Leu} (UUR) was observed in the peripheral blood leukocytes of five patients, suggesting that high-dose taurine supplementation modified the mitochondrial tRNA^{Leu} (UUR) taurine deficiency and suppressed the recurrence of the stroke-like episodes (Ohsawa et al. 2019). On the basis of these results, additional insurance coverage has been approved for this treatment in Japan. However,

a limitation of this study is the small number of patients satisfying the inclusion criteria. This means that a double-blind, placebo-controlled group could not be used in the previous clinical trials. On the other hand, a more recent study using iPSCs from a patient with MELAS has reported that MELAS iPSCs were affected by oxidative stress, and the deficits were rescued by taurine administration (Homma et al. 2021).

Many potential treatments for MELAS have been proposed and are currently in different stages of development. The mechanisms of action for these drugs are different and include decreasing ROS production, increasing NO production, enhancing mitochondrial biogenesis (nicotinamide riboside), and stabilizing the oxidized nicotinamide adenine dinucleotide modulator (Rahman and Rahman 2018). In addition, gene therapy using viral vectors to restore mitochondrial function has exhibited great potential in studies with animal models. The ultimate purpose of the gene therapy is the alternation of the heteroplasmy in the tRNA mutation model, sending the functional protein to the tissue with mutations of the respiratory chain subunit and correcting the mitochondrial defect through the use of viral vectors. A Phase III clinical trial of gene therapy is currently being conducted on patients with LHON, which is caused by mutations in the mitochondrially encoded *MT-ND4* gene, and great expectations exist for the future, as these diseases are currently untreatable and devastating (Guy et al. 2017; Montano et al. 2021).

Conclusions

A quarter of a century has passed since the A3243G point mutation in the *MT-TL1* gene, which is a typical causative gene for MELAS, was identified, and various pathological mechanisms are now being elucidated. Mitochondrial disease has a complicated pathological condition and is different from other hereditary diseases in numerous aspects, such as having the same gene mutation but different phenotypes. Several mechanisms can interact to result in stroke-like episodes in MELAS, including neuronal hyperexcitability, mitochondrial angiopathy, neuron–astrocyte uncoupling, and NO deficiency. However, in recent years, progress has been made toward the development of specific treatment methods. Because high-dose taurine supplementation modified the mitochondrial tRNA^{Leu} (UUR) taurine deficiency and suppressed the recurrence of stroke-like episodes in patients with MELAS, taurine administration has been a new practical and therapeutic approach for MELAS in the clinical setting. Due to the fact that this disease is still untreatable and devastating, many drugs are currently being tested, and new gene therapies hold great promise for the future. It is hoped that the results of forthcoming research can lead to an improvement in the quality of life for patients with MELAS.

Abbreviations CT: Computed tomography; MRI: Magnetic resonance imaging; MELAS: Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; LHON: Leber's hereditary optic neuropathy; mtDNA: Mitochondrial DNA; ATP: Adenosine triphosphate; FLAIR: Fluid-attenuated inversion recovery; DWI: Diffusion-weighted image; SPECT: Single-photon emission CT; ASL-MRI: Arterial spin labeling MRI; MRA: Magnetic resonance angiography; ANLS: Astrocytneuron lactate shuttle; NO: Nitric oxide; NOS: Nitric oxide synthase; ROS: Reactive oxygen species; iPSCs: Induced pluripotent stem cells; GC: Guanylate cyclase; GTP: Converts guanosine triphosphate; GMP: Guanosine monophosphate; Cyt c: Cytochrome c

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Data availability The authors declare that data supporting the findings of this study are available within the article. The datasets are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Declarations

Ethical approval Not applicable.

Informed consent to participate A written parental consent was obtained for publication of the MRI and CT material that is inserted in Figs. 1 and 3.

Consent for publication All authors have read the manuscript and given their consent for publication.

Conflict of interest Authors declare no conflicts of interest.

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